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An Empirical Evaluation of Hierarchical Feature Selection Methods for Classification in Bioinformatics Datasets with Gene Ontology-based Features

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Abstract Hierarchical feature selection is a new research area in machine learning/data mining, which consists of performing feature selection by exploiting dependency relationships among hierarchically structured features. This paper evaluates four hierarchical feature selection methods, i.e., HIP, MR, SHSEL and GTD, used together with four types of lazy learning-based classifiers, i.e., Naïve Bayes (NB), Tree Augmented Naïve Bayes (TAN), Bayesian Network Augmented Naïve Bayes (BAN) and k-Nearest Neighbors (KNN) classifiers. These four hierarchical feature selection methods are compared with each other and with a well-known "flat" feature selection method, i.e., Correlation-based Feature Selection (CFS). The adopted bioinformatics datasets consist of aging-related genes used as instances and Gene Ontology terms used as hierarchical features. The experimental results reveal that the HIP (Select Hierarchical Information Preserving Features) method performs best overall, in terms of predictive accuracy and robustness when coping with data where the instances' classes have a substantially imbalanced distribution. This paper also reports a list of the Gene Ontology terms that were most often selected by the HIP method.

Keywords Hierarchical Feature Selection · Classification · Machine Learning · Data Mining · Bayesian Classifiers · K-Nearest Neighbors · Biology of Aging

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1 Introduction

In the context of the classification task of machine learning (or data mining), feature selection methods aim at improving the predictive performance of classifiers by removing redundant or irrelevant features (Liu and Motoda 1998). Feature selection is a challenging problem because the number of candidate feature subsets grows exponentially with the number of features. More precisely, the number of candidate feature subsets is $2^m - 1$, where m is the number of features. Feature selection methods can be divided into two categories (Guyon and Elisseeff 2003): embedded and pre-processing methods. Embedded methods select features during the construction of the classification model. Pre-processing methods are categorized into two groups: filter and wrapper. Filter methods select features by measuring the relevance of features regardless of the classifier, whereas wrapper methods measure the relevance of features based on the performance of a classifier. In general, filter methods are faster and more scalable than wrapper methods, so we focus on filter methods in this work.

This paper addresses a specific type of feature selection problem where the features are organized into a hierarchical structure, with more generic features representing ancestors of more specific features in the feature hierarchy. In this work the feature hierarchy is the Directed Acyclic Graph (DAG) of the Gene Ontology (GO), which, broadly speaking, contains terms specifying the hierarchical functions of genes. More precisely, in our datasets, each instance is an aging-related gene (i.e., a gene which is believed to affect the process of aging in model organisms), each feature represents a GO term (broadly speaking, a gene function) that may be present or absent for each instance (gene), and the class variable specifies whether the gene is associated with increasing or decreasing the longevity of a model organism.

Note that, although we focus on feature DAGs, the methods evaluated here are also applicable to feature trees, and in general to any hierarchical feature structure where there is an "is-a" or "generalization-specialization" relationship among features, so that the presence of a feature in an instance implies the presence of all ancestors of that feature in the instance.

It is worth mentioning that the Gene Ontology is a very popular bioinformatics resource to specify gene functions, and analyzing data about aging-related genes is important because old age is the greatest risk factor for a large number of diseases (Tyner et al 2002; de Magalhães 2013). In addition, in the context of machine learning, there are a limited number of papers reporting GO terms as a type of features used for classification. In particular, in the context of aging-related gene classification, when using GO terms and other types of features, Freitas et al. (2011) classified DNA repair genes into two categories, i.e., aging-related or non-aging related; and Fang et al. (2013) classified aging-related genes into DNA repair or non-DNA repair genes. However, such methods treated GO terms as "flat" features, ignoring their hierarchical generalization-specialization relationships.

There has been very little research so far on hierarchical feature selection

methods – i.e., on feature selection methods that exploit the generalization-specialization relationships in the feature hierarchy to decide which features should be selected – for the classification task. Such hierarchical feature selection methods have been proposed in (Ristoski and Paulheim 2014; Lu et al 2013; Wang et al 2003; Jeong and Myaeng 2013). Most of these methods worked with tree-structured feature hierarchies (where a feature has at most one parent in the hierarchy) and text mining applications where instances represent documents/news and features represent words/concepts. An exception is (Lu et al 2013), where instances represent patients and features represent a tree-structured drug ontology. By contrast, in this work we address the more complex DAG-structured feature hierarchies of the GO, where a feature node can have multiple parents. Hierarchical feature selection methods have also been proposed for the task of selecting "enriched" Gene Ontology terms (terms that occur significantly more often than expected by chance) (Alexa et al 2006), which is quite different from the classification task addressed in this paper.

As far as we know, our previous work reported in (Wan and Freitas 2013; Wan et al 2015; Wan 2015; Fernandes et al 2016) seems to be the first work that proposed hierarchical feature selection methods to cope with the DAG-structured hierarchies of GO terms in the classification task. In that work we proposed three hierarchical feature selection methods, which were used as pre-processing methods for selecting features for the Naïve Bayes classification algorithm. In this paper we further evaluate the two best performing out of those three feature selection methods (reviewed in Section 3) on experiments with more types of GO terms, as well as comparing those two methods with three other feature selection methods. More precisely, this current paper extends our previous work in several directions, as follows.

First, we compare two hierarchical feature selection methods proposed in (Wan and Freitas 2013; Wan et al 2015) against two other hierarchical feature selection methods, i.e. SHSEL (Ristoski and Paulheim 2014) and GTD (Lu et al 2013). In addition, we compare those four hierarchical feature selection methods against a well-known "flat" (non-hierarchical) feature selection method, i.e., the Correlation-based Feature Selection algorithm (Hall 1998), used as a baseline method. Second, we further evaluate the hierarchical feature selection methods following the pre-processing approach with 4 classifiers, namely 3 Bayesian network classifiers – Naïve Bayes, TAN (Tree Augmented Naïve Bayes) and BAN (Bayesian Network Augmented Naïve Bayes) classifiers – and the K-Nearest Neighbors Classifier (KNN). By contrast, in (Wan and Freitas 2013; Wan et al 2015) we used only Naïve Bayes and KNN, and in (Wan and Freitas 2015) we used only BAN. Third, we evaluate all the above feature selection methods on 28 datasets of aging-related genes: 4 model organisms times 7 different sets of hierarchical features. The hierarchical features used in this work involve combinations of three types of Gene Ontology terms describing gene properties (biological process, molecular function and cellular component terms); whilst the hierarchical features used in (Wan and Freitas 2013; Wan et al 2015) involve only biological process terms.

In summary, to the best of our knowledge this paper is the first work to report the results of such an extensive evaluation of hierarchical feature selection methods for the classification task.

This paper is organized as follows. Section 2 briefly reviews the background about Naïve Bayes, TAN, BAN, KNN, lazy learning, Gene Ontology and hierarchical redundancy. Section 3 describes two hierarchical feature selection methods, viz. HIP and MR. Section 4 presents the experimental methodology and computational results, which are discussed in detail in Section 5. Section 6 reports the GO terms most frequently selected by the best feature selection method (HIP – Select Hierarchical Information Preserving Features). Finally, Section 7 presents conclusions and future research directions.

2 Background

2.1 The Naïve Bayes (NB) Classifier

Naïve Bayes (NB) is a well-known Bayesian classifier which is very computationally efficient and has in general good predictive performance. NB is based on the assumption that features are independent from each other, given the class variable. An example network topology is shown in Figure 1(a), where the edges indicate that each feature depends only on the class (their only parent node). To classify a testing instance, NB computes the probability of each class label c given all the feature values (x_1, x_2,..., x_m) of the instance using Equation (1) – where the symbol $\propto$ means "proportional to" – and assigns the instance to the class label with the greatest probability.

$$\mathbf{P}(c|x_1, x_2, ..., x_m) \propto \mathbf{P}(c) \prod_{i=1}^{m} \mathbf{P}(x_i|c) \quad (1)$$

In Equation (1), m is the number of features, and the probability of a class label c given all feature values of an instance is estimated by calculating the product of the prior probability of c times the probability of each feature value x_i given c, using the above mentioned independence assumption.

2.2 The Tree Augmented Naïve Bayes (TAN) Classifier

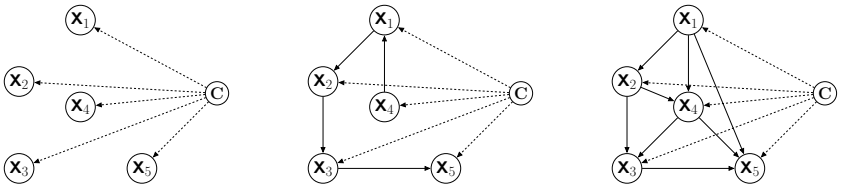
TAN is a type of semi-Naïve Bayes classifier that relaxes Naïve Bayes' feature independence assumption, by allowing each feature to depend on at most one other feature – in addition to depending on the class, which is a parent node of all features. An example network topology is shown in Figure 1(b), where all nodes except X_4 have one non-class variable parent node. This increases the ability to represent feature dependencies (which may lead to improved predictive accuracy) and still leads to reasonably efficient algorithms. TAN algorithms are not as efficient (fast) as NB, but TAN algorithms are in general much more efficient and scalable than other Bayesian classification algorithms that allow a feature to depend on several features. Among the several types of TAN algorithms, e.g., in (Friedman et al 1997; Keogh and Pazzani 1999; Jiang

et al 2005; Zhang and Ling 2001), in this work we focus on one of the most computationally efficient ones, which is based on the principle of maximizing the conditional mutual information (CMI) for each pair of features given the class attribute (Friedman et al 1997). Then, the Maximum Weight Spanning Tree (MST) is built, where the weight of an edge is given by its CMI. Finally, one vertex of the MST is randomly selected as the root, and the edge directions are propagated accordingly.

2.3 The Bayesian Network Augmented Naïve Bayes (BAN) Classifier

Compared with Naïve Bayes and TAN classifiers, a Bayesian Network Augmented Naïve Bayes (BAN) classifier is a type of more sophisticated semi-Naïve Bayes classifier that allows each feature to have more than one parents. An example network topology is shown in Figure 1(c), where node X_4 has two parent nodes, i.e., X_1 and X_2. The conventional algorithm to construct a BAN is analogous to the one for learning the TAN classifier (Friedman et al 1997).

In this work, instead of learning the feature dependencies by conventional methods, we use the GO–hierarchy–aware BAN (GO–BAN) classifier proposed in (Wan and Freitas 2013, 2015), hereafter denoted simply BAN, where the network edges representing feature dependencies are simply the pre-defined edges in the feature hierarchy. More precisely, this BAN classifier uses the edges of the Gene Ontology (GO)'s DAG (Directed Acyclic Graph) (The Gene Ontology Consortium 2000) – see Section 2.6 – as the topology of the BAN network. This has the advantages of saving computational time and exploiting the background knowledge associated with the Gene Ontology, which incorporates the expertise of a large number of biologists.



(a) NB (b) TAN (c) BAN

Fig. 1: Topology of different Bayesian network classifiers

2.4 The K-Nearest Neighbors Classifier (KNN)

K-Nearest Neighbors is a "lazy learning"-based classifier (see Section 2.5). It classifies an individual testing instance by assigning to it the class label of the majority of its k nearest training instances (Hastie et al 2001; Aha 1997; Cover and Hart 1967). In this work, the *3* nearest training instances were used for classification. We adopt the Jaccard similarity coefficient (Jain and Dubes 1988; Jain and Zongker 1997) as the distance measure, due to the fact that in the datasets used in this work the features take binary values. As shown in

Equation (2), the Jaccard similarity coefficient measures the ratio of the size of the intersection over the size of the union of two feature sets,

$$\textbf{Jaccard}(i,k) = \frac{m_{11}}{m_{11}+m_{10}+m_{01}} \quad (2)$$

where m_{11} denotes the number of features with value "1" in both the i_{th} (testing) and k_{th} (nearest training) instances; m_{10} denotes the number of features with value "1" in the i_{th} instance and value "0" in the k_{th} instance; m_{01} denotes the number of features with value "0" in the i_{th} instance and value "1" in the k_{th} instance. A greater value of the Jaccard coefficient means a smaller distance (higher similarity) between the two instances.

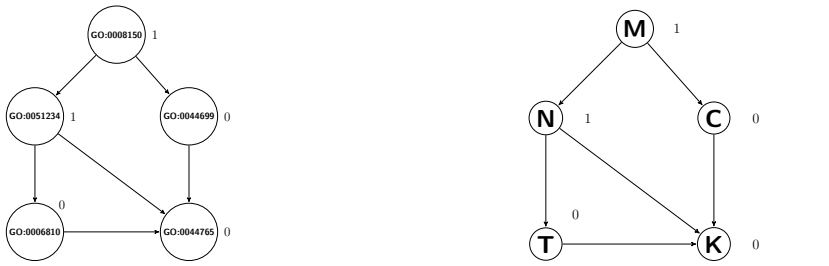
2.5 Lazy Learning

A "lazy" learning method performs the learning process in the testing phase, building a specific classification model for each new testing instance to be classified (Aha 1997; Pereira et al 2011). This is in contrast to the usual "eager" learning approach, where a classification model is learnt from the training instances before any testing instance is observed. In the context of feature selection, lazy learning selects a specific set of features for each individual testing instance, whilst eager learning selects a single set of features for all testing instances. Some hierarchical feature selection methods evaluated in this work are lazy methods, because they exploit hierarchical information which is specific to each instance, in order to select the best set of features for each instance – as described later. Hence, we use lazy versions of NB, TAN and BAN, as well as KNN (which is naturally lazy), in our experiments.

2.6 The Gene Ontology and Hierarchical Feature Redundancy

The Gene Ontology (GO) uses unified and structured controlled vocabularies to describe gene functions (The Gene Ontology Consortium 2000). There are three types of GO terms: biological process, molecular function and cellular component. Most GO terms are hierarchically structured by an "is-a" relationship, where each GO term is a specialization of its ancestor (more generic) terms. Therefore, there are three DAGs representing the three types of GO terms. For example, as shown in Figure 2(a), GO:0008150 (biological process) is the root of the DAG for biological process terms, and it is also the parent of GO:0051234 (establishment of localization), which is in turn the parent of GO:0006810 (transport).

Consider a hierarchy of features, where each feature represents a GO term which is a node in a GO DAG. Each feature takes a binary value, "1" or "0", indicating whether or not an instance (a gene) is annotated with the corresponding GO term. The "is-a" hierarchy of the GO is associated with two hierarchical constraints. First, if a feature takes the value "1" for a given instance, this implies its ancestors in the DAG also take the value "1" for that instance. For example, in Figure 2(a), if the term GO:0051234 has value "1"



(a) A small part of the Gene Ontology's topology (b) Example of hierarchical redundancy

Fig. 2: Example of hierarchically structured features

for a given gene, then the value of term GO:0008150 should be "1" as well. Conversely, if the feature takes the value "0" for a given instance, this implies that its descendants in the DAG also take the value "0" for that instance. For example, if the term GO:0006810 has value "0", then term GO:0044765 should also have value "0".

Hierarchical feature redundancy is defined in this work as the case where there are two or more nodes which have the same value ("1" or "0") in an individual instance and are located in the same path from a root to a leaf node in the DAG. For instance, in Figure 2(b), where the number "1" or "0" beside a node is the value of that feature in a given instance, nodes N and M are redundant, since both have value "1" and are located in the same path, i.e., M–N–T–K or M–N–K. Analogously, nodes T and K are redundant, since both have value "0" and are in the same path M–N–T–K. Nodes C and K are also redundant, since both have value "0" and are in the path M–C–K. Removing this type of hierarchical feature redundancy is the core task performed by the hierarchical feature selection methods used in this work.

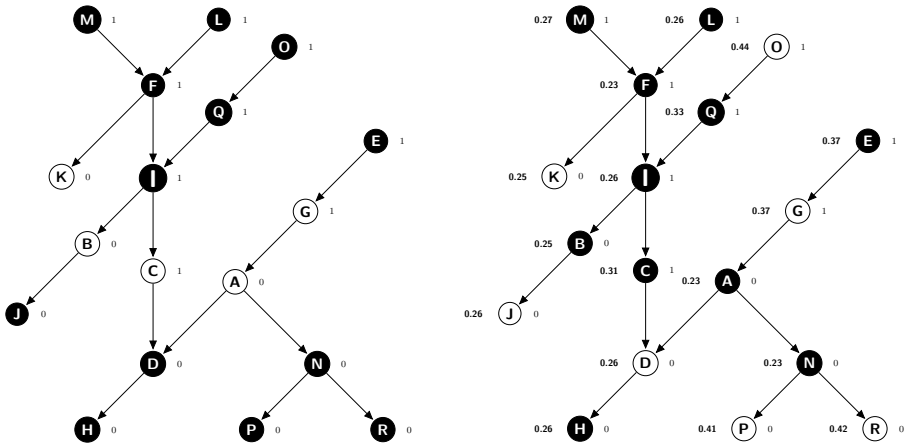
The problem of hierarchical feature selection as addressed in this paper is defined as follows: *Given a set of m features organized into a feature hierarchy (a tree or a DAG) encoding "is-a" relationships, the goal is to select a subset of s features (*$1 \leq s \leq m$*) which has reduced hierarchical redundancy, by comparison with the full set of m features, while still preserving features which are useful for discriminating among the classes.*

3 Hierarchical Feature Selection Methods – Select Hierarchical Information-Preserving (HIP) Features and Select Most Relevant (MR) Features

In our previous works (Wan and Freitas 2013; Wan et al 2015; Wan and Freitas 2015; Wan 2015), we proposed three lazy learning-based hierarchical feature selection methods to cope with the hierarchical feature redundancy issue discussed in Section 2.6. These methods are called Select Hierarchical Information-Preserving (HIP) features, Select Most Relevant (MR) features, and the hybrid HIP–MR method. In general, both HIP and MR select a set of

features without hierarchical redundancy, whereas HIP–MR usually generates a set of features where the redundancy issue is only alleviated, but not eliminated (Wan et al 2015). Hence, both HIP and MR select much fewer features, and they obtained substantially greater predictive accuracy than the hybrid HIP–MR in the experiments reported in (Wan et al 2015). Hence, we use only HIP and MR in this work.

HIP and MR perform "lazy" feature selection, i.e., they select a specific set of features for each testing instance, based on the feature values observed in that instance. The HIP method selects only features whose values are not implied by the value of any other feature in the current testing instance, due to the hierarchical constraints (see Section 2.6). For instance, in Figure 3(a), the value of node (feature) C is not implied by any other feature's value, but its value "1" implies that the values of its ancestors I, F, M, L, Q and O are also "1"; the value of node A is also not implied by any other feature's value, but its value "0" implies that the values of nodes D, H, N, P and R are also "0". HIP will select nodes K, B, C, A and G for the example DAG of Figure 3(a), since this feature subset preserves all the hierarchical information – i.e., for any given instance, the values of the features in this subset imply the values of all the other features.



(a) Features selected by HIP (b) Features selected by MR

Fig. 3: Example of hierarchical feature selection by HIP and MR

The MR method selects the feature with maximal relevance value in the set of features whose values equal to "1" or "0" in each path of the feature DAG. If there exist more than one features having the maximal relevance value, only the deepest (most specific) one (if the feature value is "1") or the shallowest (most generic) one (if the feature value is "0") in that path will be selected.

There are many different functions that can be used to evaluate the quality of a feature, such as information gain, chi-squared, etc. In the MR algorithm,

as proposed in (Wan and Freitas 2013; Wan et al 2015), Equation (3) is used to measure the relevance (**R**) (predictive power) of a binary feature X, which can take value x_1 or x_2. In this equation, n denotes the number of classes and c_i denotes the i-th class label. Equation (3) measures the relevance of a feature as a function of the difference in the conditional probabilities of each class given different values ("1" or "0") of the feature. This equation, which was adapted from a similar equation for measuring feature relevance proposed in (Stanfill and Waltz 1986), was chosen because it is simple to interpret in probabilistic terms as a direct measure of a feature's relevance for class discrimination, and so it is naturally compatible with the use of Bayesian classification network algorithms in our experiments. Future work could experiment with different feature evaluation functions.

$$\mathbf{R}(\mathrm{X}) = \sum_{i=1}^{n} [\mathbf{P}(c_i|x_1) - \mathbf{P}(c_i|x_2)]^2 \tag{3}$$

In the example DAG in Figure 3(b), where the numbers on the left side of nodes denote the corresponding relevance values and the numbers on the right side of nodes denote the binary feature values, the MR method selects 7 nodes, namely K, J, D, P, R, G and O. In detail, MR selects node O rather than node Q, since the former has higher relevance value and both nodes have the value "1" in the same path; and it selects node G rather than node E, since the former is deeper than the latter and both nodes have value "1" in the same path. Analogously, MR selects node J rather than node B, since the former has higher relevance value and both nodes have the value "0" in the same path; and it selects node D rather than node H, since the former is shallower and both nodes have value "0" in the same path. Note that, in this case, the features selected by MR will lead to some hierarchical information loss. For example, the value "1" of selected node O does not imply that the value of non-selected node Q is also "1", and the Q's value is not implied by the value of any selected node (so the information that Q has value "1" was lost). Similarly, the value "0" of selected node J does not imply that non-selected node B has value "0", and B's value is not implied by the value of any selected node.

Table 1: Summary of characteristics of the HIP and MR methods

Hierarchical FS Algorithms	**HIP**	**MR**
Merits	*Eliminate hierarchical redundancy; Retain all hierarchical information*	*Eliminate hierarchical redundancy; Select highly relevant features*
Drawbacks	*Ignore relevance of features;*	*Might lead to loss of hierarchical information*
Feature Selectivity	*Select fewer features than MR*	*Select more features than HIP*

As summarized in Table 1, both HIP and MR have the merit of eliminating hierarchical feature redundancy. However, they differ in other aspects, with their own merits and drawbacks, i.e., HIP selects features retaining all hierarchical information whilst ignoring the relevance of features with the class attribute; whereas MR selects features having higher relevance to the class attribute, but the selected features might not retain the complete hierarchical information (i.e., leading to loss of hierarchical information).

The program codes of HIP and MR (in Java) are freely available from `https://github.com/andywan0125/AIRE-Journal`.

4 Experimental Methodology and Computational Results

4.1 Dataset Creation

We constructed 28 datasets with data about the effect of genes on an organism's longevity, by integrating data from the Human Ageing Genomic Resources (HAGR) GenAge database (Build 17) (de Magalhães et al 2009) and the Gene Ontology (GO) database (version: 2014-06-13) (The Gene Ontology Consortium 2000). HAGR provides longevity-related gene data for four model organisms, i.e., *C. elegans* (worm), *D. melanogaster* (fly), *M. musculus* (mouse) and *S. cerevisiae* (yeast). For details of the dataset creation procedure, see (Wan and Freitas 2013; Wan et al 2015). However, in (Wan and Freitas 2013; Wan et al 2015) we created datasets using only Biological Process GO terms; whilst in this current work we created datasets with all three types of GO terms, each type associated with a hierarchy (see Section 2.6) in the form of a DAG: Biological Process (BP), Molecular Function (MF) and Cellular Component (CC) GO terms. Note that the different types of GO terms are contained in DAGs whose sets of nodes do not intersect with each other. This means that the hierarchical feature selection methods conduct the feature selection process based on each individual DAG separately.

Gene\GO	GO_1	GO_2	GO_3	...	GO_m	Class
Gene_1	*1*	*0*	*0*	...	*0*	*Pro*
Gene_2	*0*	*1*	*0*	...	*1*	*Anti*
Gene_3	*0*	*0*	*0*	...	*1*	*Pro*
...	...	...	...	...	...	...
Gene_n	*1*	*0*	*1*	...	*0*	*Pro*

Fig. 4: Structure of the created datasets

In the created datasets, the instances represent aging-related genes, the features represent hierarchical GO terms, and the class variable indicates whether the gene contributes to increasing or decreasing the longevity of an organism. For each model organism, we created 7 datasets, with all possible subsets of the three GO term types, i.e., one dataset for each GO term type (BP, MF, CC), one dataset for each pair of GO term types (BP and MF, BP and CC, MF and CC), and one dataset with all 3 GO term types (BP, MF and CC). The structure of each created dataset is shown in Figure 4, where the feature value "1" or "0" indicates whether or not (respectively) a GO term is annotated for each gene. In the class variable, the values "Pro" and "Anti" mean "pro-longevity" and "anti-longevity". Pro-longevity genes are those whose decreased expression (due to knock–out, mutations or RNA interference) reduces lifespan and/or whose overexpression extends lifespan. Anti-longevity genes are those whose decreased expression extends lifespan and/or whose overexpression decreases lifespan (Tacutu et al 2013).

Note that GO terms with only one associated gene would be useless for building a classification model because they are extremely specific to an individual gene, and a model that includes these GO terms would be over-fitting the data. However, GO terms associated with only a few genes might be valuable for discovering biological knowledge, since they might represent specific biological information. In our previous work (Wan et al 2015), we did experiments with different values of a threshold defining the minimum frequency of occurrence of a GO term which is required in order to include that term (as a feature) in a dataset, in order to perform effective classification. Based on that work, the threshold value of at least 3 occurrences is used here, which retains more biological information than higher thresholds while still leading to high predictive accuracy. In addition, the root GO terms – i.e., GO:0008150, GO:0003674 and GO:0005575, respectively for the DAG of biological process, molecular function and cellular component terms – are not included in the corresponding datasets, since the root GO terms have no predictive power (all genes are trivially annotated with each root GO term).

The main characteristics of the created datasets are shown in Table 2, which reports the number of features and edges in the GO DAG, the total number of instances, the number (and percentage) of instances in each class, and the degree of class imbalance. The degree of class imbalance is calculated by Equation (4), where the degree ($\mathbf{D}$) equals to the complement of the ratio of the number of instances belonging to the minority class ($\mathbf{N}^{o}(Minor)$) over the number of instances belonging to the majority class ($\mathbf{N}^{o}(Major)$).

$$\mathbf{D} = 1 - \frac{\mathbf{N}^{o}(Minor)}{\mathbf{N}^{o}(Major)} \tag{4}$$

All datasets used in our experiments are freely available from `https://github.com/andywan0125/AIRE-Journal`.

Table 2: Main characteristics of the created datasets

Caenorhabditis elegans (worm)							
Feature (GO term) type	**BP**	**MF**	**CC**	**BP+MF**	**BP+CC**	**MF+CC**	**BP+MF+CC**
Nº of Features	830	218	143	1048	973	361	1191
Nº of Edges	1437	259	217	1696	1654	476	1913
Nº of Instances	528	279	254	553	557	432	572
Nº (%) of Pro-	209	121	98	213	213	170	215
Longevity Instances	39.6%	43.4%	38.6%	38.5%	38.2%	39.4%	37.6%
Nº (%) of Anti-	319	158	156	340	344	262	357
Longevity Instances	60.4%	56.6%	61.4%	61.5%	61.8%	60.6%	62.4%
Degree of Class Imbalance	0.345	0.234	0.372	0.374	0.381	0.351	0.398
Drosophila melanogaster (fly)							
Feature (GO term) type	**BP**	**MF**	**CC**	**BP+MF**	**BP+CC**	**MF+CC**	**BP+MF+CC**
Nº of Features	698	130	75	828	773	205	903
Nº of Edges	1190	151	101	1341	1291	252	1442
Nº of Instances	127	102	90	130	128	123	130
Nº (%) of Pro-	91	68	62	92	91	85	92
Longevity Instances	71.7%	66.7%	68.9%	70.8%	71.1%	69.1%	70.8%
Nº (%) of Anti-	36	34	28	38	37	38	38
Longevity Instances	28.3%	33.3%	31.1%	29.2%	28.9%	30.9%	29.2%
Degree of Class Imbalance	0.604	0.500	0.548	0.587	0.593	0.553	0.587
Mus musculus (mouse)							
Feature (GO term) type	**BP**	**MF**	**CC**	**BP+MF**	**BP+CC**	**MF+CC**	**BP+MF+CC**
Nº of Features	1039	182	117	1221	1156	299	1338
Nº of Edges	1836	205	160	2041	1996	365	2201
Nº of Instances	102	98	100	102	102	102	102
Nº (%) of Pro-	68	65	66	68	68	68	68
Longevity Instances	66.7%	66.3%	66.0%	66.7%	66.7%	66.7%	66.7%
Nº (%) of Anti-	34	33	34	34	34	34	34
Longevity Instances	33.3%	33.7%	34.0%	33.3%	33.3%	33.3%	33.3%
Degree of Class Imbalance	0.500	0.492	0.485	0.500	0.500	0.500	0.500
Saccharomyces cerevisiae (yeast)							
Feature (GO term) type	**BP**	**MF**	**CC**	**BP+MF**	**BP+CC**	**MF+CC**	**BP+MF+CC**
Nº of Features	679	175	107	854	786	282	961
Nº of Edges	1223	209	168	1432	1391	377	1600
Nº of Instances	215	157	147	222	234	226	238
Nº (%) of Pro-	30	26	24	30	30	29	30
Longevity Instances	14.0%	16.6%	16.3%	13.5%	12.8%	12.8%	12.6%
Nº (%) of Anti-	185	131	123	192	204	197	208
Longevity Instances	86.0%	83.4%	83.7%	86.5%	87.2%	87.2%	87.4%
Degree of Class Imbalance	0.838	0.802	0.805	0.844	0.853	0.853	0.856

4.2 Experimental Methodology and Predictive Accuracy Measure

We evaluate the two previously described hierarchical feature selection methods (HIP and MR) by comparing them with two other hierarchical feature selection methods (SHSEL and GTD) and one "flat" feature selection method (CFS). In essence, the SHSEL method selects the features having more relevance and less redundancy with respect to other features in the same path in the feature hierarchy. It consists of two stages (we used the *prune*SHSEL version, see (Ristoski and Paulheim 2014)). Firstly, it starts from each leaf node of the feature hierarchy, removing the features having a relevance value similar to their parent nodes' relevance values – in this work, we adopt 0.99 as the threshold value for considering two features as similar, as suggested by (Ristoski and Paulheim 2014). Then, in the second stage, SHSEL continues to remove the features whose relevance values are less than the average relevance value for all remaining features in the corresponding path.

The GTD method is based on the greedy top-down search strategy (Lu et al 2013). It sorts features in each individual path according to their relevance values and selects the feature having the highest relevance value in each path, and then removes all other features in the path. In this work, the measure used for evaluating a feature's relevance value is the well-known Information Gain for both the SHSEL and GTD methods.

CFS is a well-known feature selection method that tries to select a feature subset where each feature has a high correlation with the class variable and the features have a low correlation with each other (to avoid selecting redundant features). Hence, CFS is an interesting baseline method because it tries to remove redundant features in a "flat" sense, without exploiting the notion of hierarchically redundant features that is at the core of HIP and MR.

Note that SHSEL, GTD and CFS follow the conventional eager learning approach, i.e., they select the same feature subset to classify all testing instances. By contrast, HIP and MR follow the lazy learning approach (see Section 2.5), performing feature selection separately for each testing instance. This gives HIP and MR the flexibility to cope with a finer-grained concept of hierarchical redundancy, which depends on each instance's specific feature values, as discussed in Section 2.6.

We perform four sets of experiments, using NB, TAN, BAN and KNN as classifiers. The well-known 10-fold cross validation procedure was adopted to evaluate the predictive performance of these classifiers with different feature selection methods. The Geometric Mean (GMean) of the Sensitivity (*Sen.*) and Specificity (*Spe.*) is used to measure predictive accuracy, since the distributions of classes in the datasets are imbalanced. As shown in Equation (5), GMean is defined as the square root of the product of *Sen.* and *Spe.*; *Sen.* denotes the percentage of positive ("pro-longevity") instances that are correctly classified as positive, whereas *Spe.* denotes the percentage of negative ("anti-longevity") instances that are correctly classified as negative.

$$GMean = \sqrt{Sen. \times Spe.} \tag{5}$$

4.3 Experimental Results

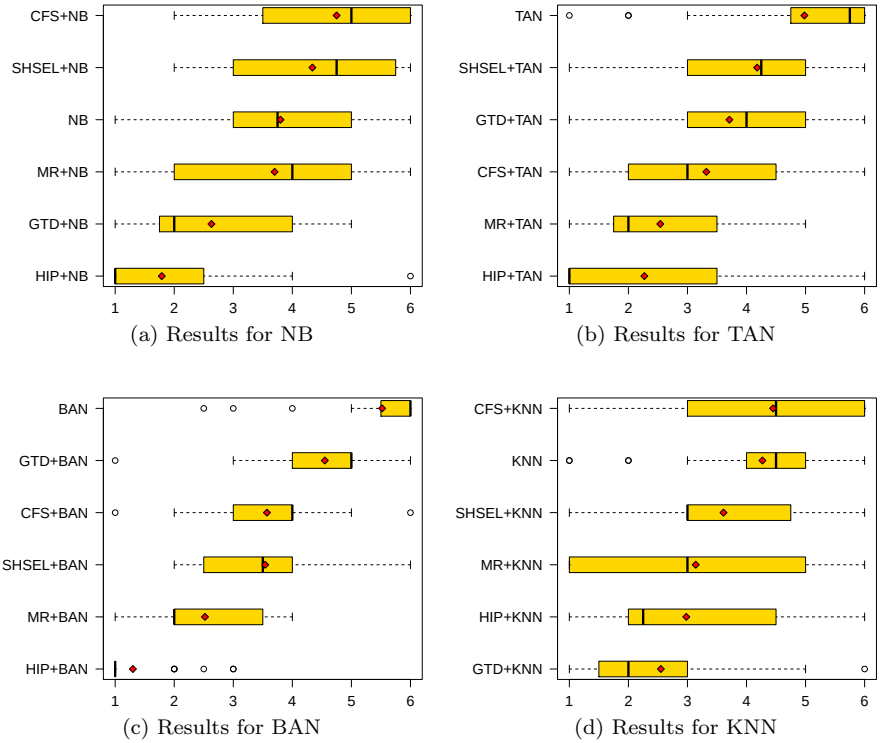
4.3.1 Feature selection results separately for each Bayesian classifier and the K-Nearest Neighbors classifier

Tables 3, 4, 5 and 6 report the feature selection results separately for each type of classifier, namely Naïve Bayes, TAN, BAN and KNN, respectively. These tables have the same structure, reporting the results for 5 different feature selection methods in a pre-processing phase, namely 4 hierarchical feature selection methods (HIP, MR, SHSEL, GTD) and the "flat" feature selection method CFS; and also reporting results for not using any feature selection method – so, 6 approaches are compared in total. Each table contains the results for 28 datasets – 7 combinations of feature (GO term) types for each of 4 model organisms. In each table, the best GMean value for each dataset is shown in boldface. For each of the 28 datasets in each table, we compute a ranking of the feature selection methods, where ranks 1 and 6 represent the best and worst GMean values, respectively, in that dataset.

The distributions of rank values (across the 28 datasets) for different feature selection methods with different classifiers are shown in the boxplots in Figures 5(a)-5(d), which summarize the results of Tables 3–6 for NB, TAN, BAN and KNN, respectively. Each boxplot consists of a box whose left and right boundaries denote the lower and upper quartile (respectively) of a distribution of rank values. The vertical line between these quartiles denotes the median rank value, the red diamond denotes the average (mean) rank value, and the horizontal lines extending from the left and the right boundaries of the box end with vertical lines that denote the smallest and highest (respectively) non-outlier rank values. Outliers are shown as separate points in the plot. The difference between the upper and lower quartiles is the inter-quartile range, and 50% of the rank values fall into this range. Note that in each of Figures 5(a)-5(d) the boxplots of different feature selection methods are sorted across the vertical axis according to their average rank – i.e., the boxplot of the method with the lowest (best) average rank is at the bottom of the figure.

Table 3 reports the predictive accuracies obtained by Naïve Bayes. As shown in Figure 5(a), HIP obtained the lowest (best) median rank (1.0) and average rank (1.8), as well as the lowest lower and upper quartiles. The interquartile range of HIP's ranks is the narrowest among all methods, indicating the small variability of its rank values across datasets. GTD+NB obtained the second best median rank (2.0) and average rank (2.6). The other methods obtained substantially worse results, with the following average and median ranks, respectively: 3.7 and 4.0 for MR, 3.8 and 3.8 for NB without feature selection, 4.3 and 4.8 for SHSEL, 4.8 and 5.0 for CFS.

Table 4 reports the predictive accuracies obtained by TAN. As shown in Figure 5(b), HIP obtained again the best median rank (1.0) and average rank (2.3); followed by MR, with median rank 2.0 and average rank 2.5. The other methods obtained substantially worse results, with the following average and median ranks, respectively: 3.3 and 3.0 for CFS, 3.7 and 4.0 for GTD, 4.2 and



(a) Results for NB (b) Results for TAN

(c) Results for BAN (d) Results for KNN

Fig. 5: Boxplots showing the distributions of ranks obtained by different feature selection methods with each of 4 classifiers

4.3 for SHSEL, 5.0 and 5.8 for TAN without feature selection.

Table 5 reports the predictive accuracies obtained by BAN. As shown in Figure 5(c), HIP obtained again the best median rank (1.0) and average rank (1.3); and it has an extremely small inter-quartile range, so even the upper quartile of its ranks is substantially lower (better) than the lower quartile of all other methods. Hence, HIP clearly outperformed all other methods, whose average and median ranks are, respectively: 2.5 and 2.0 for MR, 3.5 and 3.5 for SHSEL, 3.6 and 4.0 for CFS, 4.6 and 5.0 for GTD, 5.5 and 6.0 for BAN without feature selection.

Table 6 reports the predictive accuracies obtained by KNN. As shown in Figure 5(d), GTD obtained the best median rank (2.0) and average rank (2.6); followed by HIP, with median rank 2.3 and average rank 3.0. The other methods obtained the following average and median ranks, respectively: 3.1 and 3.0 for MR, 3.6 and 3.0 for SHSEL, 4.3 and 4.5 for KNN without feature selection, 4.5 and 4.5 for CFS.

Table 3: Predictive accuracy (%) for Naïve Bayes with hierarchical feature selection methods HIP, MR, SHSEL, GTD and "flat" feature selection method CFS

Feature Types	**NB without Feature Selection**			**HIP + NB**			**MR + NB**			**SHSEL + NB**			**GTD + NB**			**CFS + NB**		
Caenorhabditis elegans datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	50.2±3.6	69.0±2.6	58.9	54.1±3.4	75.5±2.8	63.9	51.2±3.5	75.5±2.6	62.2	50.2±4.1	74.3±2.5	61.1	63.2±4.1	65.8±2.9	**64.5**	41.1±3.3	83.7±2.6	58.7
MF	57.9±4.1	46.2±5.5	51.7	45.5±4.7	51.9±5.1	48.6	38.8±2.9	63.3±3.8	49.6	36.4±5.7	70.9±5.6	50.8	52.9±3.1	55.1±5.4	**54.0**	58.7±6.8	46.8±5.5	52.4
CC	43.9±5.7	70.5±3.4	55.6	58.2±4.9	60.9±4.0	**59.5**	42.9±4.0	71.2±3.0	55.3	34.7±3.4	76.3±3.7	51.5	46.9±5.0	67.9±3.6	56.4	35.7±4.3	74.4±3.9	51.5
BP+MF	54.0±1.8	70.3±3.0	61.6	53.5±3.6	76.2±1.9	63.8	62.9±3.5	73.2±1.8	**67.9**	51.2±3.5	75.6±1.8	62.2	61.5±3.2	67.4±2.7	64.4	50.2±3.5	77.1±2.4	62.2
BP+CC	52.6±3.9	68.3±2.6	59.9	57.7±3.7	73.0±2.6	**64.9**	55.4±2.8	73.8±2.2	63.9	49.3±2.6	73.5±2.4	60.2	57.3±3.7	70.1±2.1	63.4	44.6±3.7	77.0±2.2	58.6
MF+CC	51.2±2.8	64.1±4.3	57.3	54.7±3.3	66.0±4.1	**60.1**	47.6±3.6	68.3±4.2	57.0	42.4±3.4	73.7±3.5	55.9	52.4±2.7	66.4±4.7	59.0	47.1±3.9	72.1±3.8	58.3
BP+MF+CC	52.1±4.4	70.0±2.3	60.4	55.3±3.6	71.7±2.7	**63.0**	55.8±3.6	70.6±2.4	62.8	49.8±4.4	70.9±2.3	59.4	54.4±3.5	69.2±2.3	61.4	51.6±4.4	74.8±2.1	62.1
Drosophila melanogaster datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	74.7±3.5	36.1±9.5	51.9	73.6±4.1	44.4±9.0	**57.2**	79.1±4.1	38.9±11.0	55.5	74.7±5.2	41.7±9.6	55.8	75.8±3.8	41.7±7.9	56.2	76.9±4.7	27.8±7.4	46.2
MF	82.4±4.6	35.3±8.6	53.9	69.1±6.1	52.9±7.3	**60.5**	80.9±4.2	44.1±7.6	59.7	77.9±5.5	41.2±8.3	56.7	83.8±5.4	35.3±6.4	54.4	86.8±4.0	35.3±7.2	55.4
CC	87.1±4.1	50.0±10.2	66.0	80.6±6.5	46.4±11.4	61.2	83.9±5.6	53.6±8.7	67.1	85.5±3.9	25.0±5.1	46.2	88.7±4.3	53.6±11.2	**69.0**	87.1±3.3	39.3±10.0	58.5
BP+MF	77.2±3.9	50.0±10.2	62.1	72.8±5.6	57.9±9.3	**64.9**	79.3±4.3	44.7±8.2	59.5	81.5±3.8	44.7±9.2	60.4	77.2±3.6	42.1±6.5	57.0	85.9±3.7	31.6±7.5	52.1
BP+CC	76.9±5.1	48.6±9.8	61.1	73.6±4.9	64.9±8.3	**69.1**	80.2±4.3	56.8±11.2	67.5	79.1±3.4	45.9±8.7	60.3	76.9±4.6	48.6±9.8	61.1	82.4±3.7	43.2±10.9	59.7
MF+CC	89.4±3.2	57.9±5.3	71.9	82.4±6.1	63.2±6.7	72.2	83.5±4.4	57.9±7.5	69.5	88.2±3.5	50.0±5.3	66.4	91.8±3.5	57.9±5.3	**72.9**	91.8±3.4	42.1±8.4	62.2
BP+MF+CC	81.5±5.3	55.3±8.2	67.1	76.1±4.9	68.4±5.3	**72.1**	77.2±4.5	63.2±7.7	69.9	84.8±3.4	57.9±8.4	70.1	78.3±4.7	57.9±6.5	67.3	90.2±3.1	47.4±8.7	65.4
Mus musculus datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	82.4±4.7	44.1±5.9	60.3	72.1±4.8	70.6±5.1	**71.3**	80.9±5.2	50.0±7.9	63.6	85.3±4.3	47.1±7.0	63.4	83.8±5.0	44.1±5.9	60.8	83.8±4.0	38.2±5.6	56.6
MF	69.2±7.4	48.5±11.2	57.9	78.5±4.4	45.5±12.2	**59.8**	83.1±4.1	39.4±10.7	57.2	83.1±4.5	30.3±11.8	50.2	81.5±5.5	42.4±11.1	58.8	80.0±5.2	36.4±10.5	54.0
CC	75.8+2.3	52.9+10.0	**63.3**	80.3+3.0	47.1+11.2	61.5	81.8+3.6	41.2+11.9	58.1	77.3±3.3	50.0±10.1	62.2	75.8±2.3	52.9±10.0	**63.3**	71.2+3.0	35.3+11.2	50.1
BP+MF	83.8±3.4	44.1±7.0	60.8	70.6±4.8	70.6±8.1	**70.6**	82.4±4.2	50.0±10.2	64.2	86.8±4.0	47.1±7.7	63.9	83.8±4.5	44.1±7.0	60.8	88.2±4.2	41.2±8.0	60.3
BP+CC	79.4±6.1	50.0±8.4	63.0	66.2±5.0	73.5±9.3	**69.8**	73.5±5.1	52.9±9.6	62.4	82.4±5.1	55.9±10.5	67.9	77.9±5.7	52.9±9.6	64.2	83.8±5.0	50.0±11.3	64.7
MF+CC	75.0±5.0	64.7±12.5	**69.7**	79.4±4.2	58.8±11.8	68.3	83.8±5.0	55.9±13.3	68.4	86.8±4.6	50.0±11.7	65.9	76.5±5.1	58.8±13.0	67.1	77.9±4.8	47.1±10.9	60.6
BP+MF+CC	82.4±4.2	47.1±9.3	62.3	73.5±5.1	73.5±9.8	**73.5**	85.3±4.3	50.0±6.9	65.3	86.8±4.5	55.9±7.0	69.7	83.8±4.0	47.1±9.3	62.8	83.8±3.3	52.9±6.8	66.6
Saccharomyces cerevisiae datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	40.0±8.3	84.9±3.5	58.3	63.3±6.0	78.4±3.1	**70.4**	33.3±8.6	85.9±2.9	53.5	20.0±5.4	93.0±2.1	43.1	43.4±7.1	86.5±2.9	61.3	20.0±5.4	91.4±2.6	42.8
MF	11.5±6.1	81.7±4.8	30.7	5.0±5.0	83.2±3.4	20.4	0.0±0.0	93.9±2.4	0.0	0.0±0.0	96.9±1.3	0.0	11.5±6.1	86.3±2.9	**31.5**	5.0±5.0	92.4±1.8	21.5
CC	25.0±7.1	86.2±3.0	46.4	29.2±10.2	82.9±4.2	**49.2**	20.8±6.9	91.9±2.7	43.7	20.8±7.5	89.4±2.6	43.1	25.0±7.1	87.0±3.2	46.6	20.8±7.5	94.3±1.7	44.3
BP+MF	33.3±11.1	85.4±1.7	53.3	76.7±7.1	74.0±3.3	**75.3**	23.3±5.1	89.1±2.5	45.6	30.0±9.2	92.2±2.1	52.6	46.7±10.2	88.0±1.6	64.1	33.3±9.9	90.6±1.5	54.9
BP+CC	53.3±8.9	85.8±3.0	67.6	70.0±7.8	79.4±3.2	**74.6**	40.0±8.3	84.8±2.7	58.2	30.0±6.0	92.6±2.0	52.7	53.3±5.4	89.2±2.6	69.0	40.0±8.3	91.2±1.8	60.4
MF+CC	34.5±10.5	87.3±2.1	54.9	31.0±8.0	82.2±3.5	50.5	17.2±6.3	89.8±2.3	39.3	13.8±6.3	91.4±1.7	35.5	34.5±9.2	89.8±1.3	**55.7**	13.8±6.3	91.9±1.9	35.6
BP+MF+CC	36.7±9.2	85.6±2.7	56.0	70.0±10.5	75.0±2.6	**72.5**	30.0±9.2	86.5±2.6	50.9	49.8±4.4	70.9±2.3	59.4	54.4±3.5	69.2±2.3	61.4	36.7±10.5	92.8±1.9	58.4

Table 4: Predictive accuracy (%) for TAN with hierarchical feature selection methods HIP, MR, SHSEL, GTD and "flat" feature selection method CFS

Feature Types	TAN without Feature Selection			HIP + TAN			MR + TAN			SHSEL + TAN			GTD + TAN			CFS + TAN		
Caenorhabditis elegans datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	34.0±3.2	79.6±2.3	52.0	52.2±2.3	67.7±3.5	59.4	55.0±2.4	73.0±1.8	**63.4**	36.8±3.9	79.0±1.5	53.9	44.0±3.6	78.4±2.7	58.7	45.9±3.7	79.3±2.2	60.3
MF	37.2±5.8	61.4±5.0	47.8	43.0±5.6	50.6±4.5	46.6	33.1±3.5	65.2±4.0	46.5	25.6±4.6	74.7±5.9	43.7	43.8±3.8	61.4±5.1	**51.9**	24.8±4.8	74.7±4.0	43.0
CC	39.8±3.0	78.2±2.2	**55.8**	44.9±2.7	62.2±4.7	52.8	37.8±3.4	74.4±2.7	53.0	34.7±3.4	76.3±3.6	51.5	39.8±3.0	74.4±2.4	54.4	34.7±4.3	76.9±3.2	51.7
BP+MF	35.2±1.9	80.3±2.2	53.2	54.5±3.2	72.1±2.4	62.7	61.0±4.3	71.8±2.3	**66.2**	40.8±3.6	81.8±2.0	57.8	42.3±3.9	79.7±0.9	58.1	46.0±3.2	80.6±2.0	60.9
BP+CC	42.7±3.1	81.7±2.7	59.1	59.2±3.9	69.2±2.9	64.0	56.3±3.0	77.3±2.2	**66.0**	39.0±2.7	79.1±2.1	55.5	48.4±3.1	79.9±2.8	62.2	45.1±2.8	80.8±2.0	60.4
MF+CC	40.6±3.4	74.4±3.6	55.0	45.3±2.2	67.2±3.5	55.2	45.9±3.8	70.6±3.0	56.9	38.8±2.5	76.0±3.2	54.3	45.3±3.8	71.0±2.7	56.7	47.1±3.5	73.7±3.5	**58.9**
BP+MF+CC	39.5±2.8	80.1±2.6	56.2	60.0±5.5	71.4±2.2	**65.5**	54.4±4.2	76.5±2.3	64.5	37.2±3.6	77.6±2.5	53.7	48.4±4.1	78.4±2.4	61.6	45.6±5.0	77.3±2.2	59.4
Drosophila melanogaster datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	92.3±2.9	19.4±8.4	42.3	58.2±6.5	72.2±5.4	**64.8**	76.9±3.6	50.0±9.6	62.0	83.5±2.9	36.1±8.8	54.9	90.1±3.1	22.2±7.5	44.7	79.1±5.1	25.0±5.9	44.5
MF	91.2±3.3	20.6±5.0	43.3	73.5±5.5	32.4±7.1	48.8	83.8±4.5	41.2±7.4	**58.8**	79.4±4.3	35.3±9.5	52.9	85.3±4.3	35.3±7.9	54.9	85.3±4.3	32.4±7.1	52.6
CC	90.3±3.6	32.1±11.6	53.8	79.0±3.6	50.0±11.3	**62.8**	75.8±6.6	42.9±8.3	57.0	79.0±5.5	25.0±5.1	44.4	87.1±4.1	39.3±11.6	58.5	87.1±3.8	42.9±10.2	61.1
BP+MF	92.4±3.3	23.7±6.9	46.8	52.2±4.0	73.7±5.8	**62.0**	80.4±2.8	47.4±9.5	61.7	87.0±3.2	39.5±9.3	58.6	87.0±3.1	26.3±6.5	47.8	85.9±2.9	31.6±5.3	52.1
BP+CC	86.8±4.0	18.9±7.6	40.5	59.3±5.7	67.6±7.2	**63.3**	82.4±3.8	40.5±8.0	57.8	80.2±3.1	37.8±10.3	55.1	85.7±3.7	32.4±7.7	52.7	79.1±5.0	48.6±10.4	62.0
MF+CC	90.6±3.3	31.6±5.0	53.5	76.5±4.9	60.5±9.3	68.0	72.9±6.4	52.6±6.9	61.9	88.2±3.6	39.5±4.1	59.0	88.2±3.5	42.1±5.3	60.9	89.4±3.8	52.6±5.8	**68.6**
BP+MF+CC	92.4±2.4	18.4±5.3	41.2	60.9±7.6	78.9±6.9	**69.3**	77.2±4.5	60.5±8.5	68.3	82.6±3.8	47.4±7.9	62.6	89.1±2.4	42.1±8.4	61.2	85.9±1.8	47.4±8.7	63.8
Mus musculus datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	89.7±3.7	41.2±4.9	60.8	42.6±5.3	73.5±7.2	56.0	73.5±7.1	50.0±10.0	60.6	80.9±6.4	47.1±7.9	61.7	85.3±5.6	47.1±5.3	**63.4**	82.4±3.6	47.1±6.2	62.3
MF	89.2±4.0	33.3±9.4	54.5	69.2±7.7	66.7±7.6	**67.9**	83.1±6.6	54.5±9.1	67.3	83.1±3.3	48.5±11.7	63.5	84.6±5.3	39.4±13.0	57.7	86.2±4.0	30.3±9.6	51.1
CC	75.8±4.4	41.2±8.3	55.9	72.7±5.1	50.0±10.1	**60.3**	74.2±4.3	44.1±9.8	57.2	86.4±5.0	35.3±11.6	55.2	71.2±3.0	38.2±9.7	52.2	75.8±3.2	38.2±12.6	53.8
BP+MF	86.8±3.4	35.3±5.4	55.4	42.6±4.9	79.4±9.3	58.2	79.4±4.3	55.9±8.6	**66.6**	79.4±3.8	55.9±8.6	**66.6**	85.3±3.7	41.2±6.6	59.3	88.2±4.2	41.2±8.0	60.3
BP+CC	88.2±3.6	47.1±9.7	64.5	48.5±4.4	82.4±6.8	63.2	70.6±5.9	58.8±8.9	64.4	75.0±6.0	55.9±9.3	**64.7**	80.9±6.0	47.1±9.7	61.7	83.8±5.0	41.2±8.7	58.8
MF+CC	88.2±4.2	41.2±10.0	60.3	63.2±3.1	64.7±12.7	63.9	82.4±3.6	55.9±11.5	**67.9**	80.9±3.6	47.1±9.9	61.7	83.8±6.9	47.1±11.3	62.8	77.9±3.8	52.9±10.8	64.2
BP+MF+CC	91.2±3.2	41.2±8.6	61.3	45.6±8.0	82.4±5.2	61.3	75.0±5.7	58.8±7.9	**66.4**	77.9±5.7	52.9±7.8	64.2	80.9±4.3	47.1±7.5	61.7	77.9±4.9	55.9±7.0	66.0
Saccharomyces cerevisiae datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	3.3±3.3	98.9±1.1	18.1	56.7±10.0	68.6±2.0	**62.4**	30.0±7.8	87.0±2.7	51.1	20.0±5.4	95.7±1.6	43.7	6.7±4.4	97.3±1.2	25.5	33.3±7.0	91.9±2.4	55.3
MF	0.0±0.0	97.7±1.2	0.0	26.9±6.2	78.6±2.7	**46.0**	0.0±0.0	87.8±2.9	0.0	0.0±0.0	96.2±1.3	0.0	0.0±0.0	96.9±1.3	0.0	5.0±5.0	94.7±1.2	21.8
CC	16.7±7.0	95.9±2.1	40.0	25.0±10.6	85.4±4.0	**46.2**	20.8±6.9	95.1±2.1	44.5	12.5±6.9	92.7±2.2	34.0	16.7±7.0	95.1±1.8	39.9	16.7±7.0	93.5±1.6	39.5
BP+MF	3.3±3.3	99.0±0.7	18.1	63.3±9.2	67.7±3.1	**65.5**	20.0±7.4	93.2±1.4	43.2	23.3±7.1	93.8±2.0	46.7	10.0±7.1	98.4±0.8	31.4	30.0±6.0	93.8±1.7	53.0
BP+CC	10.0±5.1	99.0±0.7	31.5	63.3±6.0	73.5±3.8	**68.2**	30.0±9.2	89.2±2.1	51.7	33.3±7.0	94.6±1.7	56.1	10.0±5.1	99.5±0.5	31.5	33.3±8.6	94.1±1.6	56.0
MF+CC	5.0±5.0	98.5±0.8	22.2	31.0±9.9	81.7±2.5	**50.3**	10.3±6.1	93.4±2.5	31.0	6.9±5.7	93.4±1.6	25.4	10.3±6.1	98.5±0.8	31.9	10.3±6.1	94.4±1.4	31.2
BP+MF+CC	0.0±0.0	99.0±0.6	0.0	70.0±9.2	69.7±3.0	**69.8**	36.7±9.2	89.4±2.1	57.3	13.3±7.4	94.7±1.8	35.5	48.4±4.1	78.4±2.4	61.6	33.3±9.9	91.8±2.1	55.3

Table 5: Predictive accuracy (%) for BAN with hierarchical feature selection methods HIP, MR, SHSEL, GTD and "flat" feature selection method CFS

Feature Types	BAN without Feature Selection			HIP + BAN			MR + BAN			SHSEL + BAN			GTD + BAN			CFS + BAN		
Caenorhabditis elegans datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	28.7 ± 2.2	86.5 ± 1.8	49.8	54.5 ± 3.2	73.4 ± 2.7	**63.2**	52.2 ± 3.1	74.0 ± 2.2	62.2	50.2±4.4	73.7±2.8	60.8	31.6±2.2	85.3±1.9	51.9	45.0 ± 2.6	80.9 ± 2.5	60.3
MF	34.7 ± 4.5	66.5 ± 4.5	48.0	43.8 ± 4.5	52.5 ± 5.2	48.0	35.5 ± 3.0	63.3 ± 3.4	47.4	26.4±4.0	82.3±3.8	46.6	46.3±5.4	64.6±5.3	**54.7**	31.4 ± 6.6	70.9 ± 6.0	47.2
CC	33.7 ± 4.5	81.4 ± 2.2	52.4	55.1 ± 5.0	63.5 ± 4.0	**59.2**	40.8 ± 4.3	73.1 ± 2.6	54.6	35.7±4.0	76.3±3.7	52.2	32.7±4.0	77.6±2.1	50.4	35.7 ± 4.3	74.4 ± 3.9	51.5
BP+MF	30.0 ± 2.7	84.7 ± 1.7	50.4	55.9 ± 3.2	74.1 ± 2.5	64.4	63.8 ± 2.2	73.2 ± 2.1	**68.3**	49.8±3.6	75.6±1.9	61.4	37.6±2.8	80.9±1.3	55.2	52.1 ± 3.7	77.6 ± 2.2	63.6
BP+CC	29.1 ± 2.1	86.6 ± 1.7	50.2	58.7 ± 3.6	72.7 ± 2.5	**65.3**	54.0 ± 2.8	74.7 ± 2.3	63.5	50.2±2.7	72.4±2.4	60.3	37.1±3.0	84.3±2.2	55.9	47.4 ± 2.7	79.1 ± 1.5	61.2
MF+CC	35.3 ± 2.9	80.2 ± 3.2	53.2	55.9 ± 3.1	64.5 ± 3.6	**60.0**	47.1 ± 3.4	70.2 ± 3.9	57.5	37.6±4.1	78.2±2.5	54.2	41.8±4.9	77.9±3.4	57.1	46.5 ± 4.1	72.1 ± 4.0	57.9
BP+MF+CC	31.2 ± 2.9	85.2 ± 1.5	51.6	58.1 ± 3.8	73.4 ± 2.6	**65.3**	55.3 ± 4.0	72.0 ± 2.6	63.1	48.4±4.2	72.3±2.4	59.2	37.2±3.3	82.6±1.9	55.4	50.7 ± 4.1	75.4 ± 2.1	61.8
Drosophila melanogaster datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	100.0 ± 0.0	0.0 ± 0.0	0.0	75.8 ± 4.4	52.8 ± 8.6	**63.3**	80.2 ± 3.5	44.4 ± 10.2	59.7	74.7±5.2	41.7±9.6	55.8	97.8±2.2	8.3±5.7	28.5	78.0 ± 4.1	25.0 ± 7.8	44.2
MF	91.2 ± 3.3	26.5 ± 3.4	49.2	64.7 ± 7.2	50.0 ± 10.0	56.9	80.9 ± 5.2	47.1 ± 9.1	**61.7**	83.8±4.5	38.2±7.9	56.6	91.2±3.3	20.6±4.8	43.3	85.3 ± 4.3	32.4 ± 7.1	52.6
CC	93.5 ± 2.6	28.6 ± 11.1	51.7	79.0 ± 6.6	46.4 ± 11.4	60.5	85.5 ± 4.6	42.9 ± 10.2	60.6	87.1±3.3	25.0±5.1	46.7	93.5±2.6	32.1±11.6	54.8	88.7 ± 3.5	46.4 ± 11.4	**64.2**
BP+MF	97.8 ± 1.5	0.0 ± 0.0	0.0	72.8 ± 3.9	63.2 ± 9.3	**67.8**	80.4 ± 3.7	44.7 ± 8.2	59.9	82.6±4.2	42.1±8.5	59.0	97.8±1.5	5.3±3.3	22.8	83.7 ± 3.5	28.9 ± 6.2	49.2
BP+CC	98.9 ± 1.1	0.0 ± 0.0	0.0	73.6 ± 4.7	62.2 ± 8.4	**67.7**	80.2 ± 4.1	51.4 ± 10.9	64.2	79.1±3.4	45.9±8.7	60.3	95.6±2.5	8.1±3.8	27.8	82.4 ± 4.4	40.5 ± 10.2	57.8
MF+CC	95.3 ± 1.9	31.6 ± 5.3	54.9	80.0 ± 6.2	60.5 ± 7.6	**69.6**	83.5 ± 4.9	55.3 ± 8.2	68.0	89.4±3.2	47.4±5.8	65.1	91.8±3.7	47.4±5.8	66.0	90.6 ± 3.0	52.6 ± 4.5	69.0
BP+MF+CC	98.9 ± 1.1	2.6 ± 2.5	16.0	73.9 ± 4.7	68.4 ± 5.3	71.1	81.5 ± 3.7	63.2 ± 7.7	**71.8**	84.8±3.4	60.5±8.5	71.6	97.8±1.5	7.9±5.5	27.8	88.0 ± 2.6	44.7 ± 8.2	62.7
Mus musculus datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	98.5 ± 1.4	26.5 ± 5.0	51.1	75.0 ± 5.1	70.6 ± 5.1	**72.8**	88.2 ± 4.7	44.1 ± 7.7	62.4	85.3±4.3	47.1±7.0	63.4	98.5±1.4	38.2±4.7	61.3	85.3 ± 4.3	44.1 ± 5.9	61.3
MF	90.8 ± 3.3	27.3 ± 10.0	49.8	84.6 ± 3.0	45.5 ± 12.2	**62.0**	87.7 ± 3.0	39.4 ± 10.6	58.8	83.1±4.5	30.3±11.8	50.2	87.7±3.0	33.3±12.5	54.0	87.7 ± 2.9	30.3 ± 9.6	51.5
CC	86.4 ± 3.3	35.3 ± 11.2	55.2	80.3 ± 3.0	50.0 ± 10.1	**63.4**	78.8 ± 3.8	44.1 ± 11.1	58.9	77.3±3.3	50.0±10.1	62.2	81.8±3.9	44.1±11.1	60.1	78.8 ± 3.3	38.2 ± 12.6	54.9
BP+MF	98.5 ± 1.4	29.4 ± 6.4	53.8	69.1 ± 5.8	70.6 ± 8.1	**69.8**	86.8 ± 4.0	41.2 ± 9.6	59.8	86.8±4.0	47.1±7.7	63.9	97.1±1.9	35.3±7.0	58.5	89.7 ± 2.2	41.2 ± 8.0	60.8
BP+CC	98.5 ± 1.4	29.4 ± 6.4	53.8	66.2 ± 6.0	76.5 ± 8.0	**71.2**	77.9 ± 5.3	52.9 ± 9.6	64.2	82.4±5.1	55.9±10.5	67.9	98.5±1.4	41.2±7.9	63.7	82.4 ± 5.6	47.1 ± 11.7	62.3
MF+CC	91.2 ± 3.2	26.5 ± 8.8	49.2	79.4 ± 4.2	61.8 ± 12.5	70.0	83.8 ± 5.0	58.8 ± 13.1	**70.2**	86.8±4.6	41.2±10.2	59.8	89.7±3.2	41.2±11.0	60.8	79.4 ± 4.8	44.1 ± 9.6	59.2
BP+MF+CC	98.5 ± 1.4	26.5 ± 10.5	51.1	70.6 ± 6.0	76.5 ± 8.8	**73.5**	86.8 ± 4.0	50.0 ± 6.9	65.9	86.8±4.5	55.9±7.0	69.7	97.1±1.9	35.3±10.2	58.5	83.8 ± 3.3	52.9 ± 8.4	66.6
Saccharomyces cerevisiae datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	0.0 ± 0.0	100.0 ± 0.0	0.0	63.3 ± 6.0	76.8 ± 3.1	**69.7**	33.3 ± 8.6	89.7 ± 2.5	54.7	20.0±5.4	93.0±2.1	43.1	0.0±0.0	100.0±0.0	0.0	20.0 ± 5.4	94.6 ± 1.9	43.5
MF	0.0 ± 0.0	99.2 ± 0.8	0.0	23.1 ± 6.7	80.2 ± 3.9	**43.0**	0.0 ± 0.0	90.8 ± 3.0	0.0	0.0±0.0	97.7±1.2	0.0	0.0±0.0	98.5±1.0	0.0	0.0 ± 0.0	94.7 ± 1.6	0.0
CC	12.5 ± 6.1	99.2 ± 0.8	35.2	29.2 ± 10.2	83.7 ± 4.1	**49.4**	20.8 ± 6.9	93.5 ± 2.7	44.1	16.7±7.6	90.2±2.5	38.8	16.7±7.0	96.7±1.3	40.2	20.8 ± 7.5	93.5 ± 1.6	44.1
BP+MF	0.0 ± 0.0	100.0 ± 0.0	0.0	73.3 ± 6.7	71.9 ± 3.0	**72.6**	23.3 ± 7.1	89.6 ± 2.6	45.7	30.0±9.2	92.7±2.2	52.7	0.0±0.0	100.0±0.0	0.0	26.7 ± 8.3	96.4 ± 1.1	50.7
BP+CC	0.0 ± 0.0	100.0 ± 0.0	0.0	63.3 ± 10.5	78.4 ± 2.9	**70.4**	40.0 ± 8.3	87.3 ± 2.5	59.1	33.3±7.0	92.6±2.3	55.5	0.0±0.0	100.0±0.0	0.0	26.7 ± 6.7	96.6 ± 1.1	50.8
MF+CC	0.0 ± 0.0	100.0 ± 0.0	0.0	41.4 ± 8.3	80.7 ± 3.0	**57.8**	13.8 ± 6.3	88.8 ± 2.3	35.0	13.8±6.3	91.4±1.7	35.5	3.4±0.0	99.0±0.7	18.3	13.8 ± 6.3	93.4 ± 1.5	35.9
BP+MF+CC	0.0 ± 0.0	100.0 ± 0.0	0.0	76.7 ± 7.1	73.6 ± 2.8	**75.1**	33.3 ± 5.0	87.0 ± 2.5	53.8	20.0±7.4	90.4±2.3	42.5	0.0±0.0	100.0±0.0	0.0	23.3 ± 8.7	94.2 ± 1.6	46.8

Table 6: Predictive accuracy (%) for KNN (k=3) with hierarchical feature selection methods HIP, MR, SHSEL, GTD and "flat" feature selection method CFS

Feature Types	KNN without Feature Selection			HIP + KNN			MR + KNN			SHSEL + KNN			GTD + KNN			CFS + KNN		
Caenorhabditis elegans datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	48.3±4.8	74.0±3.0	59.8	51.7±2.8	77.4±3.5	**63.3**	47.4±2.9	73.4±2.2	59.0	54.1±3.3	65.2±3.2	59.4	48.8±5.2	73.7±3.0	60.0	63.6±3.5	49.5±4.3	56.1
MF	41.3±3.3	54.4±4.4	47.4	36.4±4.4	53.2±4.5	44.0	40.5±4.0	62.0±5.9	**50.1**	32.2±7.4	69.0±7.2	47.1	37.2±4.1	58.2±3.7	46.5	16.5±3.1	75.9±2.9	35.4
CC	39.8±6.5	67.9±3.3	52.0	40.8±4.0	68.6±2.9	52.9	34.7±7.5	64.1±1.9	47.2	32.7±5.2	69.2±6.1	47.6	45.9±6.2	67.3±2.7	**55.6**	35.7±4.6	65.4±4.7	48.3
BP+MF	49.3±3.5	72.9±1.2	59.9	52.6±3.4	74.1±1.7	**62.4**	49.3±3.1	74.7±1.9	60.7	56.3±3.5	64.1±3.8	60.1	50.2±4.9	76.8±1.9	62.1	65.3±4.1	50.6±4.3	57.5
BP+CC	42.7±3.4	72.7±2.7	55.7	45.1±3.2	77.0±1.9	58.9	43.7±4.3	74.1±2.2	56.9	51.2±3.5	67.7±2.8	58.9	45.5±3.4	74.1±3.1	58.1	67.1±2.6	53.2±5.9	**59.7**
MF+CC	44.7±2.7	68.3±2.6	55.3	47.1±2.5	71.4±2.9	58.0	44.7±2.0	67.9±3.1	55.1	48.8±4.4	66.8±4.1	57.1	47.6±2.2	71.0±2.6	**58.1**	40.6±4.2	75.2±2.7	55.3
BP+MF+CC	47.9±3.6	72.0±2.4	58.7	47.4±3.9	75.1±1.7	59.7	48.8±4.3	74.5±1.5	**60.3**	47.4±2.5	65.8±3.2	55.8	46.5±2.3	74.8±2.5	59.0	59.1±4.2	51.3±3.9	55.1
Drosophila melanogaster datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	80.2±4.9	38.9±7.5	55.9	84.6±3.8	50.0±10.0	65.0	68.1±5.4	63.9±8.3	**66.0**	62.6±7.3	58.3±9.0	60.4	78.0±4.4	52.8±7.5	64.2	49.5±4.6	69.4±7.9	58.6
MF	77.9±5.6	32.4±5.2	50.2	69.1±5.7	44.1±7.0	55.2	61.8±5.2	41.2±5.5	50.5	55.9±5.0	58.8±7.0	**57.3**	76.5±5.6	35.3±3.7	52.0	27.9±4.8	70.6±7.6	44.4
CC	83.9±5.6	46.4±10.0	62.4	82.3±4.7	46.4±12.2	61.8	79.0±6.2	53.6±12.4	**65.1**	64.5±5.2	60.7±11.2	62.6	83.9±6.1	50.0±12.4	64.8	50.0±5.0	53.6±7.5	51.8
BP+MF	79.3±5.1	42.1±9.9	57.8	78.3±4.7	52.6±9.7	64.2	71.7±4.4	57.9±7.5	**64.4**	67.4±5.1	50.0±8.7	58.1	78.3±6.6	44.7±9.0	59.2	51.1±3.6	68.4±7.5	59.1
BP+CC	78.0±5.4	37.8±8.9	54.3	83.5±3.0	51.4±6.0	65.5	78.0±3.2	56.8±7.3	**66.6**	65.9±4.1	48.6±7.9	56.6	78.0±5.0	51.4±7.4	63.3	56.0±4.8	64.9±8.1	60.3
MF+CC	91.8±3.1	42.1±6.7	62.2	82.4±5.2	57.9±5.3	**69.1**	76.5±6.8	44.7±8.4	58.5	74.1±4.1	52.6±4.5	62.4	89.4±4.0	47.4±7.3	65.1	43.5±4.7	71.1±7.3	55.6
BP+MF+CC	81.5±3.8	52.6±6.9	65.5	84.8±3.0	63.2±7.7	**73.2**	80.4±4.6	63.2±9.3	71.3	72.8±3.4	52.6±4.5	61.9	81.5±4.4	52.6±8.7	65.5	60.9±4.3	73.7±6.5	67.0
Mus musculus datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	86.8±3.4	41.2±4.7	59.8	82.4±5.9	64.7±8.8	**73.0**	86.8±4.0	47.1±8.9	63.9	85.3±4.8	50.0±13.4	65.3	88.2±4.2	47.1±7.2	64.5	86.8±3.4	35.3±8.8	55.4
MF	78.5±4.5	39.4±10.4	55.6	89.2±5.1	39.4±8.1	59.3	84.6±3.3	45.5±10.0	**62.0**	84.6±3.9	42.4±13.5	59.9	83.1±5.7	45.5±8.7	61.5	89.2±3.1	30.3±9.4	52.0
CC	74.2±7.7	41.2±9.4	55.3	75.8±4.4	38.2±10.2	53.8	65.2±6.4	50.0±9.0	**57.1**	80.3±5.7	35.3±9.3	53.2	71.2±6.4	32.4±9.9	48.0	74.2±4.3	38.2±10.2	53.2
BP+MF	83.8±4.0	47.1±7.3	62.8	83.8±4.0	52.9±11.7	66.6	86.8±4.0	55.9±8.2	**69.7**	85.3±2.1	52.9±6.7	67.2	85.3±3.7	55.9±7.3	69.1	85.3±4.3	44.1±8.1	61.3
BP+CC	86.8±5.8	47.1±10.1	63.9	77.9±5.3	50.0±9.1	62.4	86.8±4.0	58.8±6.8	**71.4**	82.4±3.6	50.0±6.0	64.2	88.2±5.6	55.9±8.8	70.2	85.3±3.0	41.2±8.6	59.3
MF+CC	77.9±4.3	61.8±6.9	**69.4**	80.9±4.8	50.0±8.9	63.6	73.5±4.7	50.0±11.6	60.6	86.8±5.0	41.2±7.6	59.8	79.4±5.7	55.9±9.2	66.6	75.0±4.7	52.9±11.9	63.0
BP+MF+CC	83.8±4.5	50.0±10.8	64.7	85.3±6.4	55.9±8.5	69.1	80.9±3.7	58.8±10.8	69.0	86.8±5.0	58.8±8.8	**71.4**	83.8±4.5	47.1±9.7	62.8	86.8±3.3	41.2±9.6	59.8
Saccharomyces cerevisiae datasets																		
	Sen.	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*	*Sen.*	*Spe.*	*GM*
BP	10.0±5.1	95.7±1.9	30.9	10.0±5.1	91.4±1.8	30.2	26.7±8.3	92.4±2.3	49.7	16.7±5.6	93.0±1.8	39.4	30.0±9.2	94.1±1.7	**53.1**	23.3±5.1	94.1±2.2	46.8
MF	11.5±6.9	90.1±3.0	32.2	3.8±0.0	96.2±1.3	19.1	7.7±4.4	91.6±1.8	26.6	11.5±6.1	93.9±2.5	32.9	15.4±7.0	90.1±1.7	37.2	19.2±6.9	91.6±1.4	**41.9**
CC	12.5±6.9	93.5±2.1	34.2	12.5±6.9	93.5±2.1	34.2	12.5±6.9	93.5±2.0	34.2	12.5±6.1	96.7±1.3	34.8	20.8±11.7	87.8±3.1	**42.7**	16.7±7.0	93.5±2.4	39.5
BP+MF	13.3±5.4	94.8±1.8	35.5	16.7±7.5	93.8±1.5	39.6	26.7±6.7	95.8±1.3	50.6	23.3±8.7	93.8±1.7	46.7	30.0±6.0	94.3±1.8	**53.2**	23.3±8.7	94.8±1.1	47.0
BP+CC	20.0±5.4	96.6±1.1	44.0	26.7±6.7	97.1±0.8	50.9	16.7±5.6	92.6±1.8	39.3	33.3±7.0	93.6±1.7	55.8	33.3±7.0	95.6±1.4	**56.4**	30.0±7.8	97.1±0.8	54.0
MF+CC	17.2±8.0	94.9±1.3	**40.4**	13.8±11.4	95.9±1.7	36.4	13.8±6.3	94.9±1.7	36.2	10.3±6.1	92.4±1.8	30.8	10.3±6.1	95.9±1.3	31.4	17.2±8.0	91.4±1.7	39.6
BP+MF+CC	20.0±7.4	95.7±1.1	43.7	30.0±9.2	97.1±1.5	54.0	13.3±7.4	94.7±1.5	35.5	23.3±7.1	95.2±1.7	47.1	33.3±9.9	94.7±1.3	**56.2**	20.0±7.4	95.7±1.7	43.7

4.3.2 Global comparison of all 24 pairs of a feature selection method and a classifier

This section considers each pair of a feature selection approach combined with a type of classifier as a whole "classification approach", and compares the predictive performance of the 24 classification approaches used in our experiments, rather than evaluating the results of each feature selection approach separately for each type of classifier like in the previous section. Note that we have 24 classification approaches because there are 6 feature selection approaches (5 feature selection methods and the no feature selection approach) and 4 classifiers. Figure 6 shows the boxplots displaying the distribution of ranks (based on Gmean values) for each classification approach, across the 28 datasets. Table 7 shows the number of wins (where the highest GMean value was obtained) by each classification approach.

HIP+BAN achieved the best results among all classification approaches, with median rank 2.0, average rank 3.3, and 22 wins. HIP+NB achieved the second best results, with median rank 2.0, average rank 3.9 and 19 wins. Clearly both HIP+BAN and HIP+NB obtained substantially better results than all other 22 classification approaches, as shown in Figure 6 and Table 7. The third best approach in Figure 6 was GTD+NB, with median rank 6.0 and average rank 7.3. The third best approach in Table 7 was HIP+TAN, with 15 wins. In addition, looking at the last row of Table 7, with the total number of wins for each feature selection method across all four classifiers, HIP was clearly the best method with 61 wins, followed by MR with 22 wins and GTD with 17 wins.

Table 7: Number of wins (best Gmean values) obtained by each combination of a feature selection approach and a classifier

# Wins	HIP	MR	SHSEL	GTD	CFS	NoFS
NB	19	1	0	7	0	2
TAN	15	7	2	2	2	1
BAN	22	4	0	1	1	0
KNN	5	10	2	7	2	2
Σ Wins	**61**	22	4	17	5	5

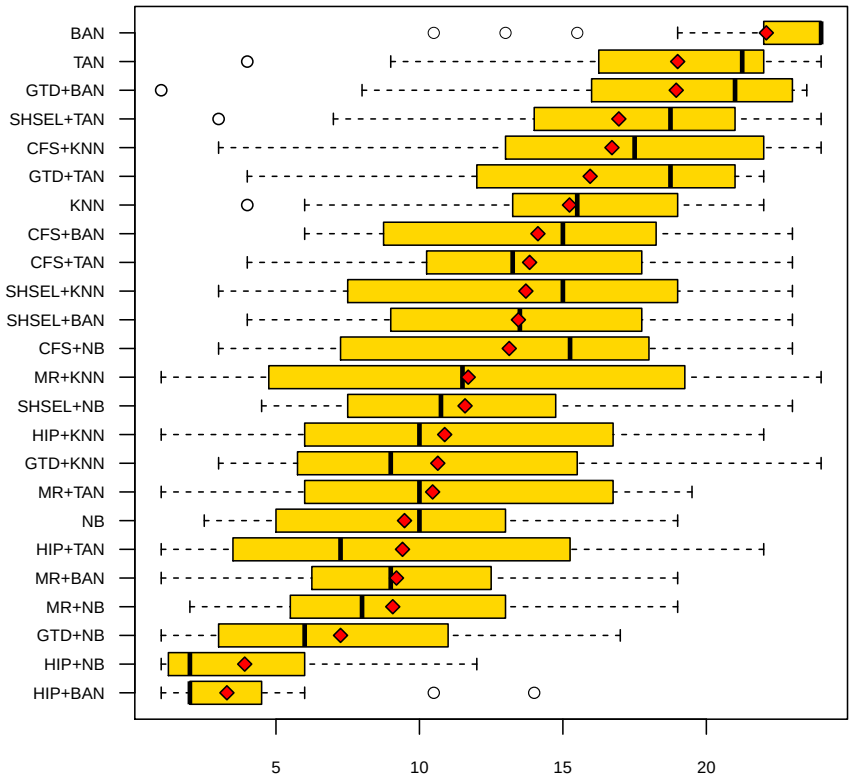


Fig. 6: Boxplots showing the distributions of ranks obtained by 24 classification approaches across all 28 datasets

5 Discussion

5.1 Results of Statistical Significance Tests on Predictive Accuracy

We adopted the Friedman test, followed by the Holm *post-hoc* test, to conduct statistical significance tests on the differences between the GMean values of the feature selection methods, when using NB, TAN, BAN and KNN as classifiers. The Friedman test is a non-parametric statistical test based on the ranks of each classifier's GMean value on each dataset (Japkowicz and Shah 2011; Derrac et al 2011). The Friedman test determines whether or not the differences between the results of the methods being compared as a whole are significant. If they are, then the Holm *post-hoc* test is adopted to cope with the multiple hypothesis testing problem when using significance tests, by adjust-

Table 8: Holm *post-hoc* test results for the methods' GMean values

NB				**TAN**			
FS Method	*Ave. Rank*	*P-Value*	*Adjusted α*	*FS Method*	*Ave. Rank*	*P-Value*	*Adjusted α*
HIP+NB (ctrl.)	1.79	N/A	N/A	HIP+TAN (ctrl.)	2.27	N/A	N/A
GTD+NB	2.63	**9.30E-02**	5.00E-02	MR+TAN	2.54	**5.89E-01**	5.00E-02
MR+NB	3.70	1.33E-04	2.50E-02	CFS+TAN	3.32	**3.57E-02**	2.50E-02
NB	3.80	5.82E-05	1.67E-02	GTD+TAN	3.71	3.98E-03	1.67E-02
SHSEL+NB	4.34	3.40E-07	1.25E-02	SHSEL+TAN	4.18	1.33E-04	1.25E-02
CFS+NB	4.75	3.22E-09	1.00E-02	TAN	4.98	5.96E-08	1.00E-02
BAN				**KNN**			
FS Method	*Ave. Rank*	*P-Value*	*Adjusted α*	*FS Method*	*Ave. Rank*	*P-Value*	*Adjusted α*
HIP+BAN (ctrl.)	1.30	N/A	N/A	GTD+KNN (ctrl.)	2.55	N/A	N/A
MR+BAN	2.52	1.47E-02	5.00E-02	HIP+KNN	2.98	**3.90E-01**	5.00E-02
SHSEL+BAN	3.54	7.46E-06	2.50E-02	MR+KNN	3.14	**2.38E-01**	2.50E-02
CFS+BAN	3.57	5.63E-06	1.67E-02	SHSEL+KNN	3.61	**3.40E-02**	1.67E-02
GTD+BAN	4.55	8.03E-011	1.25E-02	KNN	4.27	5.82E-04	1.25E-02
BAN	5.52	3.17E-017	1.00E-02	CFS+KNN	4.45	1.45E-04	1.00E-02

ing the significance level (α) for pairwise method comparisons (Demsăr 2006). The Holm test compares a control feature selection method (the best method) against each of the other methods. All uses of the Friedman test in our analyses indicated a significant difference between the methods being compared as a whole (in all cases the p-value was smaller than 0.001), so we report next the detailed results of the uses of the Holm *post-hoc* test.

We firstly applied significance tests on the results for different feature selection approaches working with each of the four classifiers (results for experiments in Section 4.3.1). The Holm tests results are shown in Table 8. The difference between average GMean ranks between the best (control) method and another method is considered significant if, in the row for that latter method, the *P-value* is smaller than the *Adjusted* α. The few non-significant results are highlighted in boldface in Table 8.

As shown in the top-left 4 columns in Table 8, when working with NB, HIP obtained the best predictive accuracy and significantly outperformed 4 of the other 5 methods, the exception being GTD.

The top-right 4 columns show that when working with TAN, HIP obtained again the best predictive accuracy, which is not significantly different from the accuracy of MR and CFS, but is significantly better than the accuracy of the other 3 methods.

The bottom-left 4 columns show that when working with BAN, HIP obtained the best predictive accuracy and significantly outperformed all other 5 methods.

The bottom-right 4 columns show that when working with KNN, GTD obtained the best predictive accuracy, but it significantly outperformed only the worst two methods (CFS and KNN without feature selection), i.e., there was no significant difference between the accuracies of GTD, HIP, MR and SHSEL.

Table 9: Holm *post-hoc* test results comparing 24 classification approaches

Classification approach	**Average rank**	**P-value**	**Adjusted α**
HIP+BAN (ctrl.)	3.29	N/A	N/A
HIP+NB	3.91	**7.43E-01**	5.00E-02
GTD+NB	7.25	**3.62E-02**	2.50E-02
MR+NB	9.07	2.22E-03	1.67E-02
MR+BAN	9.20	1.77E-03	1.25E-02
HIP+TAN	9.41	1.20E-03	1.00E-02
NB	9.48	1.06E-03	8.33E-03
MR+TAN	10.46	1.48E-04	7.14E-03
GTD+KNN	10.64	1.01E-04	6.25E-03
HIP+KNN	10.88	5.92E-05	5.56E-03
SHSEL+NB	11.59	1.12E-05	5.00E-03
MR+KNN	11.70	8.59E-06	4.55E-03
CFS+NB	13.13	1.92E-07	4.17E-03
SHSEL+BAN	13.45	7.62E-08	3.85E-03
SHSEL+KNN	13.71	3.51E-08	3.57E-03
CFS+TAN	13.84	2.36E-08	3.33E-03
CFS+BAN	14.13	9.69E-09	3.13E-03
KNN	15.23	2.65E-10	2.94E-03
GTD+TAN	15.95	2.10E-11	2.78E-03
CFS+KNN	16.71	1.24E-12	2.63E-03
SHSEL+TAN	16.95	4.90E-13	2.50E-03
GTD+BAN	18.95	1.16E-16	2.38E-03
TAN	19.00	9.33E-17	2.27E-03
BAN	22.09	2.57E-23	2.17E-03

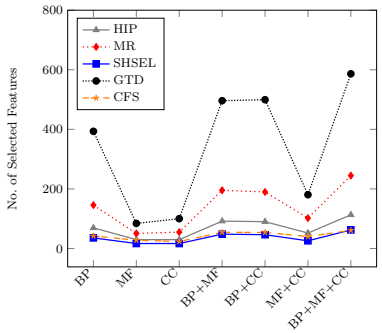
We then applied significance tests to the results of all 24 classification approaches – all pairs of a feature selection approach and a classifier. The results for the Holm test are shown in Table 9, where the only two non-significant results are highlighted in boldface. As shown in this Table, the Holm test results indicate that the predictive accuracy of the best classification approach, namely HIP+BAN (with average rank 3.29), is significantly better than the accuracies of 21 of the other 23 approaches. The only two exceptions are the accuracies of the second best approach, HIP+NB (with average rank 3.91), and the third best approach, GTD+NB (with average rank 7.25). The reason why the large difference between the average rank of HIP+BAN (3.29) and GTD+NB (7.25) was not significant according to the Holm test seems to be the multiple hypothesis testing problem associated with executing this test 23 times. Interestingly, in Table 9 the two worst classification approaches are BAN and TAN without feature selection; but when these classifiers are combined HIP, the resulting classification approaches become the best and the sixth best approaches (respectively), out of all the 24 approaches. This is

further evidence of the effectiveness of the HIP feature selection method.

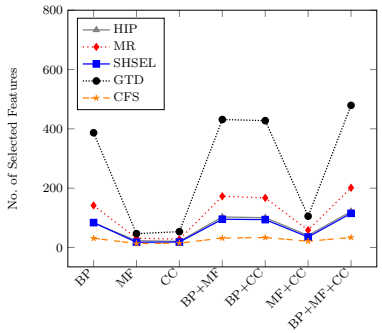
In summary, HIP was clearly the best feature selection method overall. As shown in Table 7, it obtained the best predictive performance in 61 cases, followed by 22 wins for MR and 17 wins for GTD, considering all four classifiers. Also, the classification approaches of HIP+BAN and HIP+NB obtained much lower (better) average ranks than all the other 22 classification approaches, and HIP+BAN obtained statistically significantly better predictive accuracies than 21 classification approaches.

5.2 Results Regarding the Numbers of Selected Features

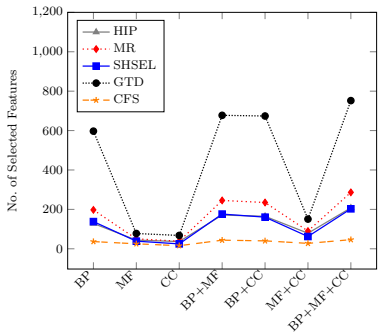
Figures 7(a)-(d) show the number of features selected by the HIP, MR, SHSEL, GTD and CFS methods for 7 different types of datasets for each model organism, each dataset with a different set of GO term types, as explained earlier. Broadly speaking, HIP selected somewhat more features than SHSEL and CFS, but less features than MR and GTD. GTD always selected the largest number of features across the 4 model organisms.



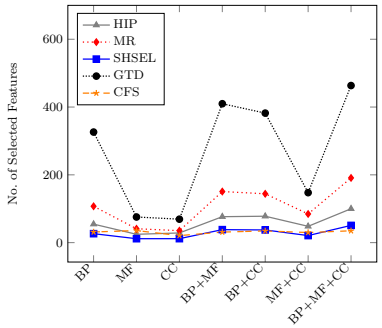
(a) *Caenorhabditis elegans* datasets



(b) *Drosophila melanogaster* datasets



(c) *Mus musculus* datasets



(d) *Saccharomyces cerevisiae* datasets

Fig. 7: Average number of features selected by HIP, MR, SHSEL, GTD and CFS for each of the feature (GO term) types

5.3 Robustness of Predictive Performance Against Imbalanced Class Distributions

As shown in Figure 8, the degree of class imbalance (calculated by Equation (4)) for the datasets range from 0.35, for the *C. elegans* datasets, to 0.84, for the *S. cerevisiae* datasets.

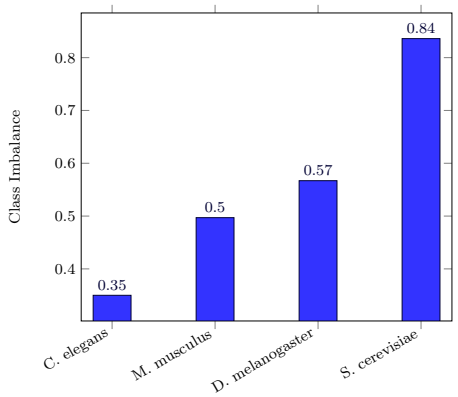


Fig. 8: Average degree of class imbalance for each of the 4 model organisms datasets – averaged over the 7 feature (GO term) types

We evaluated HIP, MR, SHSEL, GTD and CFS from the perspective of robustness of predictive performance against large degrees of class imbalance, by computing the linear correlation coefficient (r) between the degree of class imbalance (**D**) and GMean values over the 28 datasets. Note that r values close to 0 indicate that the GMean values are not influenced by the degree of class imbalance, while large negative values of r indicate that GMean values are significantly reduced as the degree of class imbalance increases.

In Figure 9, the scatter plots show the relationships between GMean and **D** values, while the red straight lines indicate the fitted linear regression models. Regarding the classification approaches without feature selection, Figures 9(a)-(d) show that the NB classifier is the most robust against class imbalance (r = –0.258), while TAN is largely negatively affected by class imbalance (r = –0.801).

When the feature selection methods work with NB, HIP (Figure 9(e)) and GTD (Figure 9(q)) improve the robustness against class imbalance, as their r values are –0.035 and –0.198 respectively. The r values for the other feature selection methods range from –0.453 to –0.483, indicating a weak robustness to class imbalance.

When the feature selection methods work with TAN, all methods enhanced the robustness of TAN against class imbalance. HIP obtained the biggest improvement over TAN without feature selection, since its r value is just 0.088. GTD had the weakest robustness to class imbalance, with r = –0.668.

Analogously, when the feature selection methods work with BAN, HIP again obtained the biggest improvement on robustness, with $r = 0.103$, whereas

GTD again obtained the weakest robustness, with r = –0.830.

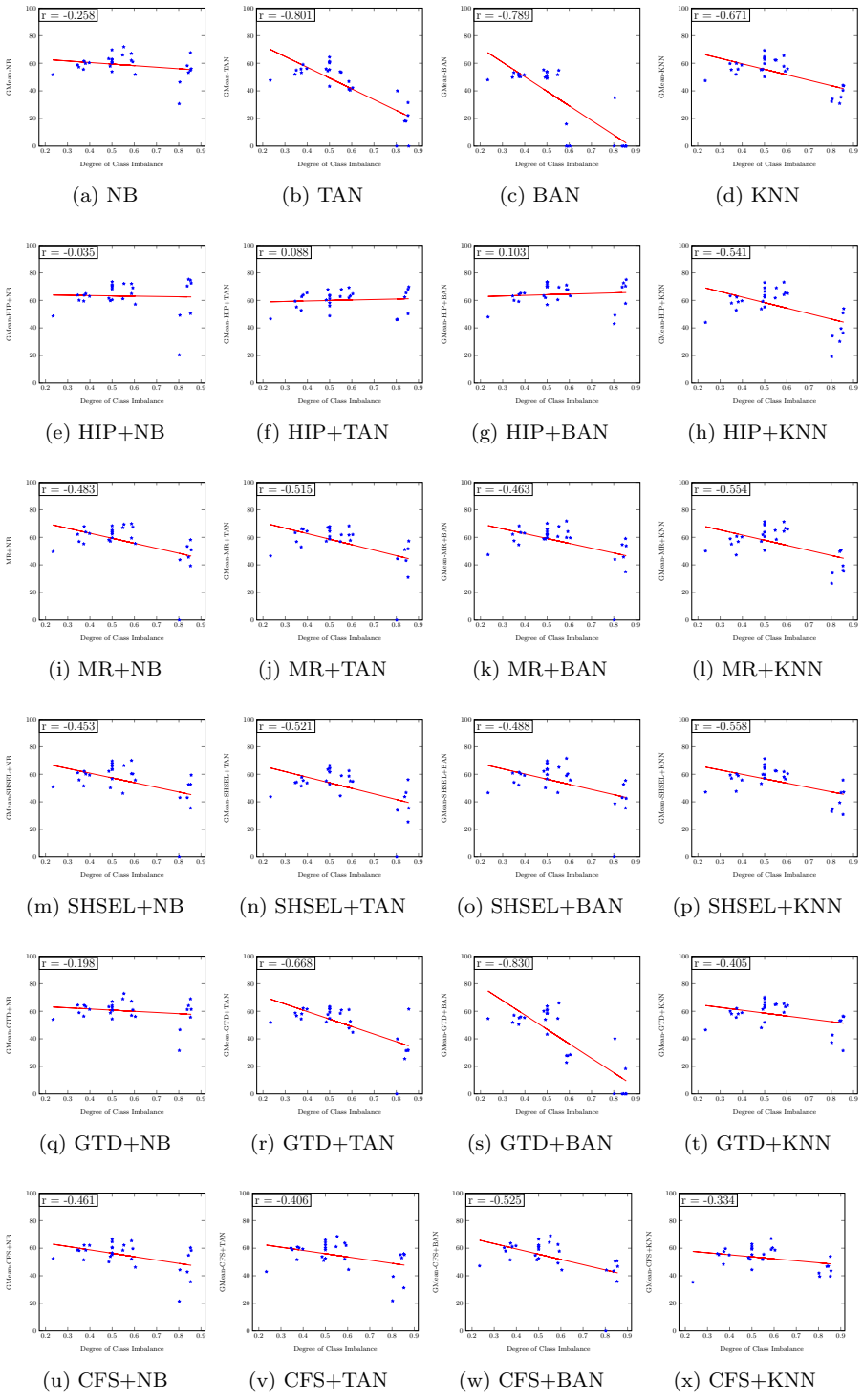
When the feature selection methods work with KNN, CFS obtained the biggest improvement on robustness, with r = –0.334. GTD obtained the second biggest improvement, with r = –0.405, while other feature selection methods obtained r values ranging from from –0.541 to –0.558.

Overall, HIP showed the strongest robustness to class imbalance, since it obtained the biggest improvements on robustness for NB, TAN and BAN classifiers, and its r values are in most cases close to "0" (indicating the strongest robustness). The other feature selection methods have in general substantially large negative values of r, which means that their predictive accuracy tends to decrease substantially with an increase on the degree of class imbalance.

The fact that HIP is much more robust to class imbalance than all other feature selection methods contributes substantially to HIP's better GMean results, as explained next. First of all, note that in general HIP, MR, SHSEL, GTD and CFS tend to achieve higher accuracy in the prediction of majority class instances than in the prediction of minority class instances. This can be seen by noting the following two general patterns (although there are exceptions) in Tables 3, 4, 5 and 6. First, HIP, MR, SHSEL, GTD and CFS exhibit in general substantially larger Specificity (Spe.) than Sensitivity (Sen.) for *C. elegans* and *S. cerevisiase* datasets, where Spe. measures the accuracy in the prediction of instances of the majority class ("anti-longevity" in these datasets). Second, HIP, MR, SHSEL, GTD and CFS exhibit in general substantially larger Sen. than Spe. for *D. melanogaster* and *M. musculus* datasets, where Sen. measures the accuracy in the prediction of instances of the majority class ("pro-longevity" in these datasets).

Next, to quantify the imbalance between Sen. and Spe. obtained by each feature selection method, we computed the difference (**Diff**) between these two terms as given by Equation (6), where *Max* and *Min* return the maximum and minimum among their two arguments, respectively. Equation (6) returns a positive value proportional to the difference ("imbalance") between Sen. and Spe. Recall that $GMean = \sqrt{Sen. \times Spe.}$, which means that in order to maximize GMean one has to find a balance between maximizing both Sen. and Spe., rather than maximizing one at the expenses of minimizing the other. Then, we further calculated the linear correlation coefficient (r) between **Diff** and the degree of class imbalance given by Equation (4), as shown in Figure 10. In this Figure, it is clear that all feature selection methods except HIP have a large positive r value, varying from 0.670 to 0.892, when working with three Bayesian classifiers; whilst when working with the KNN classifier all 5 feature selection methods have large positive values, ranging from 0.631 to 0.881. This means that, for the MR, SHSEL, GTD and CFS methods, a higher degree of class imbalance tends to lead to a large **Diff** value for all 4 classifiers. This tendency is overall much weaker for HIP, which tends to obtain more balanced Sen. and Spe. values, leading to higher GMean values than MR, SHSEL, GTD and CFS, as observed in Tables 3, 4, 5 and 6 in general.

$$\textbf{Diff} = Max(Sen, Spe) - Min(Sen, Spe) \tag{6}$$



(a) NB (b) TAN (c) BAN (d) KNN

(e) HIP+NB (f) HIP+TAN (g) HIP+BAN (h) HIP+KNN

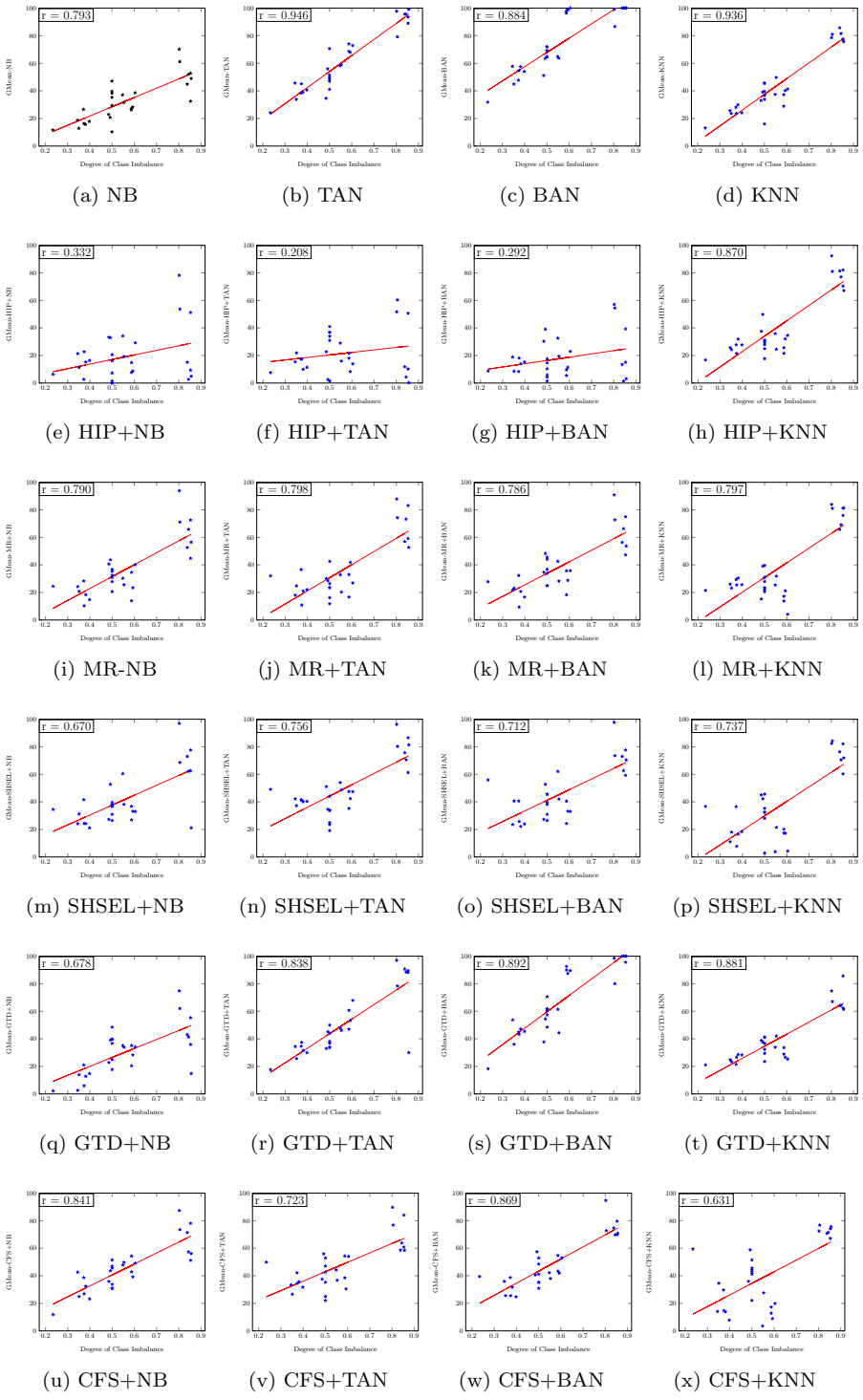
(i) MR+NB (j) MR+TAN (k) MR+BAN (l) MR+KNN

(m) SHSEL+NB (n) SHSEL+TAN (o) SHSEL+BAN (p) SHSEL+KNN

(q) GTD+NB (r) GTD+TAN (s) GTD+BAN (t) GTD+KNN

(u) CFS+NB (v) CFS+TAN (w) CFS+BAN (x) CFS+KNN

Fig. 9: Linear relationship between the degree of class imbalance and GMean values



(a) NB (b) TAN (c) BAN (d) KNN

(e) HIP+NB (f) HIP+TAN (g) HIP+BAN (h) HIP+KNN

(i) MR-NB (j) MR+TAN (k) MR+BAN (l) MR+KNN

(m) SHSEL+NB (n) SHSEL+TAN (o) SHSEL+BAN (p) SHSEL+KNN

(q) GTD+NB (r) GTD+TAN (s) GTD+BAN (t) GTD+KNN

(u) CFS+NB (v) CFS+TAN (w) CFS+BAN (x) CFS+KNN

Fig. 10: Linear relationship between **Diff** and GMean values

5.4 Computational time cost for different feature selection methods

The running times (in seconds) for different feature selection methods are reported in Table 10. In each row, the reported times refer to the running times on the largest dataset for the model organism shown in the first column, i.e. the dataset using all BP, MF and CC features. The top part of this table reports the running times to run each feature selection method in a preprocessing phase, before running a classifier. The bottom part reports the running times to run both each feature selection method and the Naïve Bayes classifier applied to the selected features. We focus on results for Naïve Bayes because this is a very computationally efficient (fast) classifier in general and it sill obtained very good predictive accuracy results with most feature selection methods – in particular, in Table 9, comparing the average rank of 24 classification approaches, 3 out of the best 5 approaches used Naïve Bayes (with HIP, GTD and MR). The running times were measured by using a *Lenovo* desktop with Intel i3-3220 CPU@3.30GHz, 8.00GB ram and 64-bit Windows 8.1 operation system.

Generally, in terms of feature selection methods only, MR and CFS had by far the longest running times for all 4 datasets. Note that, although both MR and HIP are lazy learning-based methods designed to remove hierarchical redundancy, MR is much slower than HIP, since MR (unlike HIP) has to select the feature(s) having maximum relevance value among a set of features when processing each path of the feature DAG. The other 3 methods are eager learning-based methods. Among these, CFS takes much longer to run, which

Table 10: Running time (in seconds) for 5 feature selection methods and for combinations of these methods with the NB classifier

Running time of feature selection methods only						
Dataset	HIP	MR	SHSEL	GTD	CFS	
C. elegans	494.6	31475.8	9.1	30.6	18999.9	
D. melanogaster	382.7	5462.7	6.4	28.7	6067.1	
M. musculus	605.1	6351.0	9.1	27.5	28376.9	
S. cerevisiae	406.9	10581.9	6.0	25.3	7828.8	
Running time of feature selection methods + NB						
Dataset	HIP+NB	MR+NB	SHSEL+NB	GTD+NB	CFS+NB	NB
C. elegans	698.3	32269.1	10.2	130.2	19001.0	591.0
D. melanogaster	395.6	5490.2	7.2	41.5	6067.2	42.5
M. musculus	626.9	6385.4	10.7	50.4	28377.0	71.9
S. cerevisiae	434.5	10669.7	6.3	47.4	7829.0	100.3

seems partly because it has to consider redundancy between potentially any pair of features regardless of their position in the feature hierarchy (since CFS ignores the structure of this hierarchy). By contrast, SHSEL and GTD (like HIP and MR) consider redundancy in a much more focused way, considering only the hierarchical redundancies among features in the same path. GTD takes longer to run than SHSEL (although both are fast in general), which seems mainly due to GTD's sorting process for features in each path.

Regarding the time required to run both a feature selection method and Naïve Bayes with the selected features, the results are analogous to the previous ones. That is, MR+NB and CFS+NB are by far the slowest classification approaches, due to the much longer running time of MR and CFS in the feature selection stage. Note that SHSEL+NB and GTD+NB have a shorter running time than NB without feature selection, due to NB being applied to a reduced feature subset, in those approaches. HIP+NB takes longer than NB without feature selection (since HIP is not so fast), but this increase in computational time is in general a small price to pay for the much better predictive accuracy of HIP+NB, as discussed earlier.

5.5 Summary of the Empirical Comparisons Between Hierarchical Feature Selection Methods

Overall, HIP was the best feature selection method when working with Naïve Bayes, TAN and BAN; whilst GTD was the best method when working with the KNN classifier. In addition, HIP showed the strongest robustness against class imbalance, when working with Naïve Bayes, TAN and BAN. In our previous work in (Wan et al 2015), using only biological process GO terms as features, there was no statistically significant difference between HIP and MR when working with Naïve Bayes. In this work we performed experiments with more types of GO terms used as features – viz., biological process, molecular function and cellular component, and different combinations of these types. In these extended experiments, we conclude that HIP, which eliminates hierarchical redundancy and selects the features that preserve the complete hierarchical information, performed statistically significantly better than MR, SHSEL and CFS when working with Naive Bayes. When working with TAN, HIP was significantly better than GTD and SHSEL. When working with BAN, HIP was significant better than all other feature selection methods (MR, SHSEL, CFS and GTD). When working with KNN, GTD was the best method, but it was not significantly better than HIP, MR and SHSEL. For details, see Table 8 and its corresponding discussion.

6 Identifying the GO Terms (Features) Most Often Used for Classification

As the HIP method performed best overall, we computed the ranks of GO terms selected by HIP in the BP+MF+CC datasets, for each of the 4 model

organisms. Broadly speaking, the top-ranked terms identified in this analysis are also top-ranked terms when considering the individual datasets for each feature type (BP, MF and CC) separately. The top-ranked terms are shown in Table 11. The first four columns of this table have self-explanatory names. The rank in column 5 is based on two criteria. The first one is the "Frequency of Selection" in column 6, which means the number of times the GO term was selected by HIP for classifying the testing instances. The second, tie-breaking ranking criterion is the "Frequency in Edges" in column 7, which means the number of edges containing the GO term in the trees built by TAN for classifying the test instances. Recall that, for building the tree, each feature can have at most one parent feature, but each feature can be the parent for more than one features. Hence, a feature could act as a "hub" node, if that feature is the parent for many nodes. Note that the value of "Frequency in Edges" will always be greater than or equal to the value of "Frequency of Selection", since one selected feature should be included in at least one edge.

As shown in Table 11, several GO terms were very often selected across three model organisms: Synapse (GO:0045202), Extracellular Region (GO:0005576), and Antioxidant Activity (GO:0016209) are top-ranked terms in the *Caenorhabditis elegans*, *Drosophila melanogaster* and *Mus musculus* datasets. Other GO terms were selected across two model organisms: Reproduction (GO:0000003) and Electron Carrier Activity (GO:0009055) are top-ranked in the *Caenorhabditis elegans* and *Drosophila melanogaster* datasets; Protein Binding Transcription Factor Activity (GO:0000988) in the *Caenorhabditis elegans* and *Saccharomyces cerevisiae* datasets; Receptor Activity (GO:0004872) and Enzyme Regulator Activity (GO:0030234) in the *Drosophila melanogaster* and *Saccharomyces cerevisiae* datasets.

Briefly, several of these very often selected GO terms fit well with some aging-related hypotheses. For example, oxidative processes produce byproducts, i.e., ROS (reactive oxygen species), which can cause damage and crosslink DNA (Vijg and Campisi 2008); and antioxidant activity, which can mitigate the harmful effects of high-levels of ROS and is also related to the hypothesis that calorie restriction can delay aging, was found to be able to extend the longevity of model organisms like *Caenorhabditis elegans*, *Mus musculus* and *Drosophila melanogaster* (Walker et al 2005; Wood et al 2004; Sohal and Weindruch 1996; Sohal et al 1994). As another example, in terms of the link between reproduction and aging, in *Caenorhabditis elegans*, mutations in the *daf-2* gene reduce insulin/insulin-like growth factor-1 (IGF-1) signaling and lead to extended lifespan and delayed reproduction (Kenyon 2010).

7 Conclusions

In summary, we evaluated the predictive performance of four hierarchical feature selection methods and compared them with the well-known "flat" feature selection method CFS (Correlation-based Feature Selection), by using Naïve Bayes, Tree Augmented Naïve Bayes, Bayesian Network Augmented Naïve

Table 11: Information about the GO terms most frequently selected by the HIP method

Model Organism	GO Term ID	GO Term Type	GO Term Name	Rank	Freq. of Selection	Freq. in Edges	Predicted Class
Caenorhabditis elegans	GO:0045202	CC	synapse	1	572	2394	Anti
	GO:0000003	BP	reproduction	2	572	1929	Anti
	GO:0005576	CC	extracellular region	3	572	1095	Anti
	GO:0016209	MF	antioxidant activity	4	572	697	Pro
	GO:0040007	BP	growth	5	572	633	Pro
	GO:0022610	BP	biological adhesion	6	568	1046	Pro
	GO:0000988	MF	protein binding transcription factor activity	7	567	801	Pro
	GO:0009055	MF	electron carrier activity	8	567	779	Anti
	GO:0031974	CC	membrane-enclosed lumen	9	567	769	Anti
Drosophila melanogaster	GO:0009055	MF	electron carrier activity	1	130	199	Pro
	GO:0005576	CC	extracellular region	2	130	193	Pro
	GO:0000003	BP	reproduction	3	130	184	Anti
	GO:0044456	CC	synapse part	4	130	174	Pro
	GO:0045202	CC	synapse	5	130	152	Pro
	GO:0016209	MF	antioxidant activity	6	127	354	Pro
	GO:0005198	MF	structural molecule activity	7	127	180	Pro
	GO:0030234	MF	enzyme regulator activity	8	126	144	Anti
	GO:0004872	MF	receptor activity	9	125	189	Anti
Mus musculus	GO:0044456	CC	synapse part	1	102	354	Anti
	GO:0005198	MF	structural molecule activity	2	102	344	Pro
	GO:0005576	CC	extracellular region	3	102	270	Pro
	GO:0005623	CC	cell	4	102	191	Anti
	GO:0045202	CC	synapse	5	102	124	Anti
	GO:0030054	CC	cell junction	6	99	248	Anti
	GO:0016209	MF	antioxidant activity	7	99	246	Pro
	GO:0023052	BP	signaling	8	99	207	Pro
	GO:0031012	CC	extracellular matrix	9	99	176	Pro
Saccharomyces cerevisiae	GO:0005085	MF	guanyl-nucleotide exchange factor activity	1	238	358	Anti
	GO:0004872	MF	receptor activity	2	238	282	Anti
	GO:0022414	BP	reproductive process	3	234	511	Anti
	GO:0009295	CC	nucleoid	4	234	321	Anti
	GO:0005933	CC	cellular bud	5	231	479	Anti
	GO:0000988	MF	protein binding transcription factor activity	6	231	340	Anti
	GO:0005622	CC	intracellular	7	231	283	Anti
	GO:0032126	CC	eisosome	8	231	243	Anti
	GO:0030234	MF	enzyme regulator activity	9	230	403	Anti

Bayes and k-Nearest Neighbors classifiers over 28 aging-related gene datasets where hierarchies of Gene Ontology (GO) terms were used as predictive features. The experimental results showed that in general the HIP method performed best in terms of predictive accuracy, and it showed more robustness against a large degree of class imbalance than the other feature selection methods. We further computed the ranking of GO terms based on how often they were selected by the HIP method for classifying test instances, and identified GO terms that are among the top-ranked terms for more than one model organisms.

An interesting future research direction would be to propose new hierarchical feature selection methods for coping with classification datasets where the features are non-binary – e.g., real-valued features. Another research direction would be to distinguish between the different evidence codes associated with GO term annotations in our datasets – e.g., comparing the results of using computationally inferred vs. experimentally validated GO terms (usually considered more reliable) as features.

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